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EDITORIALS

ARTICLES

VIEWPOINTS

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Improving the prescribing practice of junior doctors through interprofessional collaboration and evidence-based education

Dale Sheeha, Avril Lee, Arindam Basu, John Thwaites

This paper explains how two district health boards medical education units adapted a UK educational approach to reduce prescribing errors by junior doctors in their first year of practice, using pharmacist's expertise as clinical coaches. The impact was measured on patient care, using prescribing error data across a six-month period. The research showed that not only is it possible to accelerate prescribing performance of new prescribers, but the participants' experience was practical and relevant. The research team are currently exploring how to scale up this work for entire cohorts of junior doctors and build sustainability into the process.

What helps and hinders metformin adherence and persistence: a qualitative study exploring the views of people with type 2 diabetes

Lianne Parkin, Karyn Maclennan, Lisa Te Morenga, Marie Inder, Losa Moata'ane

Metformin is the first-line treatment for type 2 diabetes. Our wider research group recently examined national pharmaceutical dispensing data and found that metformin adherence (taking metformin as prescribed) and persistence (continuing to take metformin) varied by patient characteristics such as age and ethnicity. Although the work provided a good overview of how metformin is being used in New Zealand, it did not provide any information about patient perspectives on the enablers of, and barriers to, optimal adherence and persistence. We interviewed 10 Māori, 10 Pacific and 10 non-Māori non-Pacific patients who had started metformin within the previous two years, and we identified several barriers to metformin adherence and persistence—these included delays in accepting the diagnosis of type 2 diabetes, the cost of visiting a doctor and prescription charges, complex and busy lives and feelings of guilt and shame about having diabetes and/or poor control of blood sugars that prevented people from visiting their doctor. Participants' comments highlighted the importance of developing and maintaining good patient–healthcare provider relationships and tailoring communication styles to the preferences of patients; some Māori and Pacific participants also emphasised the importance of having Māori and Pacific healthcare providers who share their cultural identity and language.

The emergence of azole resistance in Aspergillus fumigatus complex in New Zealand

Wendy P McKinney, Anna Vesty, Jaideep Sood, Hasan Bhally, Arthur J Morris

Aspergillus fumigatus causes serious infections that are difficult to treat with high mortality. The most commonly used treatments are anti-fungal drugs called azoles. Resistance to azoles is common in some countries and we are now seeing resistant strains in New Zealand. There should be improved access (ie, funding) to appropriate antifungal agents for certain Aspergillus infections in New Zealand.

Primary medication non-adherence to analgesics and antibiotics at Counties Manukau Health Emergency Department

Nataly Martini, Bert van der Werf, Deborah Bassett-Clarke

The study investigated whether patients discharged from Counties Manukau Health Emergency Department had their prescriptions for antibiotics, paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) filled. The majority of patients in the study were New Zealand-born (67%), of Pacific Island descent (43%), living in the most socioeconomically deprived areas (78%) and under the age of 10 years (33%). Almost half of the patients in the study did not fill all of the medicines on their prescription with smokers and those aged between 10 and 44 years most likely to not to fill their prescriptions. Filling rates increased significantly if more than one medicine was prescribed. Antibiotics were most likely to be filled, and NSAIDs were significantly more likely to be filled compared with paracetamol.

Complications of endoscopically placed duodenal stents for malignant duodenal outlet obstruction

Anurag Sekra, Vijay Dyavadi, Qiuyu Jin, Ravinder Ogra

A duodenal stent is a piece of metal that is placed across blockage in the duodenum from cancer. It is placed with the help of an endoscope (flexible camera). This is a safe and extremely effective procedure to improve symptoms of blockage and our study highlights this.

Patch testing to plants: sensitisation associated with exposure to plants, essential oils and botanicals in cosmetics

Victoria L Murphy, Denesh C Patel, Steven R Lamb, Harriet S Cheng

Contact allergy to plants presents with dermatitis and is diagnosed with skin patch testing. Reactions to plant allergens were found to be related to botanicals in cosmetics and creams, plants and essential oils. Rates of plant sensitisation (positive patch-testing reactions) in our cohort are comparable with international data.

Ciguatera poisoning and confirmation of ciguatoxins in fish imported into New Zealand

J. Sam Murray, D. Tim Harwood, Lesley Rhodes

As the global need for protein is growing exponentially, countries are now looking at tropical reef fish from the Pacific region to meet this demand. In turn, this means the risk of people being exposed to ciguatera poisoning, the most common non-microbial food borne illness in the world, is rapidly growing, highlighting the importance of raising awareness of this tropical disease. One such example is the recent intoxication event that happened in Christchurch, New Zealand. Five people became ill after consuming imported Fiji Kawakawa, a commonly caught grouper species, and upon hospitalisation were clinically diagnosed as having ciguatera poisoning. Meal remnants were then tested by scientists at Cawthron Institute and confirmed the presence of ciguatoxins, the causative compounds of this poisoning syndrome.

Care planning, diagnosis and management in paediatric functional constipation

Darryl Cochrane

Paediatric constipation is a chronic condition and its treatment requires medication to keep the stool soft and behavioural interventions. A thorough history, including questions about the frequency of bowel movements and stool type, is required. If no red flags are found after examining the abdomen, spine, lower limbs and perianal area, the practitioner should have confidence to aggressively manage the constipation through a constipation action plan.

Participant injury in clinical trials conducted in New Zealand for the benefit of manufacturers: an unfair system?

Mark Bolland

When injuries occur in trials conducted in New Zealand for the benefit of the manufacturer, trial participants are excluded from ACC coverage. Injured trial participants therefore need to seek compensation from the trial sponsor. The article describes a case where a trial participant suffered a rare illness that the treating doctors thought related to participating in the trial. It took more than six years for the case to be settled and was a long and arduous process for the participant that ultimately required legal assistance. The case demonstrates that the current system is not fair for this group of trial participants and needs to change. Most of these trial participants will not be aware of the difficulties they may face if they become injured. Any change requires political input, but a simple solution would be to repeal the specific section of the current ACC Act that excludes these trials from ACC coverage, meaning all trial participants would be covered by ACC. Any costs could be met by charging trial sponsors a levy.

Anti-NMDA receptor autoimmune encephalitis

Akram Shmendi, Stewart Shiu

Anti-NMDA receptor encephalitis is a type of an autoimmune disease where the body's immune system attacks its own bod, and the body itself gets damaged by its immune system. It affects a type of receptor in the brain tissue called ‘N-Methyl D-Aspartate’ receptors, which are responsible for modulating memory, cognition and learning. Their involvement leads to many psychiatric and abnormal behavioural and personality symptoms.

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"We have been warned"—preparing now to prevent the next pandemic

David R Murdoch, Sue Crengle, Bob Frame,
Nigel P French, Patricia C Priest

'COVID-19: Make it the Last Pandemic' is the aspirational title of the recently released report by the Independent Panel for Pandemic Preparedness and Response.[1] This panel, co-chaired by Helen Clark and Ellen Johnson Sirleaf, was convened in mid-2020 by the World Health Organization (WHO) to assess the global handling of COVID-19.

The report is predictably grim reading. The panel found weak links at every point in the chain of preparedness and response. Preparation was inconsistent and underfunded, alert systems were too slow and meek, WHO was under-powered, responses exacerbated inequities and global leadership was absent.

Although giving the world a clear 'fail' for its handling of COVID-19, the report highlights strengths upon which to build. Of particular note, successful national responses to COVID-19 were often built on lessons from previous outbreaks. Those countries listened to the science, changed course when necessary, engaged communities and communicated transparently and consistently. In Aotearoa New Zealand, responses to lessons from the past were most evident among Māori, who were prompted to look after their own communities with knowledge of experiences during previous outbreaks, such as the smallpox epidemic of 1913 and the influenza pandemic in 1918-9.[2,3]

The report of the Independent Panel for Pandemic Preparedness and Response makes two sets of recommendations.

The first set includes immediate actions aimed at ending the COVID-19 pandemic, with a particular emphasis on addressing global inequities. Unsurprisingly, a major focus is a push for greater commitment from high-income countries to increase global access to vaccines, diagnostics and therapeutics, and to help strengthen health systems.

The second set of recommendations comprise seven actions directed at preparedness to ensure that a future outbreak does not become a pandemic:

1. Pandemic preparedness and response must be elevated to the highest level of political leadership in all countries and globally, with the establishment of a Global Health Threats Council.
2. WHO should have more independence, authority and funding.
3. Pandemic preparedness needs investment from now to prevent the next crisis by creating fully functional capabilities at national, regional and global levels.
4. A new agile and rapid surveillance information and alert system is needed.
5. A global platform should be built for equitable development and distribution of vaccines, therapeutics, diagnostics and essential supplies.
6. A new mechanism for international financing for pandemic preparedness and response should be created.
7. Finally, national pandemic coordinators with a direct line to heads of state or government should be established.

These are good recommendations. However, they have already been criticised for not going far enough, particularly with respect to strengthening international agreements and country commitments.[4]

Aotearoa New Zealand certainly must play its part in strengthening and ensuring global commitment to both ending the current COVID-19 pandemic and preparedness for the future. We can build on our good international standing to strengthen global solidarity and help resist counterproductive activities, such as hoarding COVID-19 vaccines by rich countries, including through continued support to Pacific countries with vaccine supply.

But we must also look to our own planning and future response. What can we take from the report to inform our own planning for the future?

We need to act now with national preparedness planning, not wait until after the current pandemic or for the next crisis. The history of pandemics reminds us that we have failed to learn from past experiences.[5] We need to reverse this trend and start preparing for the future, informed by the lessons and impacts from COVID-19 while fresh in our minds.

Māori and other groups who experience inequities must be involved in all pandemic preparedness activities and in planned responses to ensure these are equity-positive and prevent the development or exacerbation of existing inequities.

We need to develop and invest in good leadership at all levels, forward-looking rather than reactive, and in the critical partnership of science, policy and leadership.

Aotearoa New Zealand has done relatively well so far in its response to COVID-19, but this does not guarantee continued success as this pandemic plays out, or similar success in future pandemics. We cannot be complacent and must do better in preparing for future infectious diseases risks. We must do better at joining up our expertise and systems and break down unhelpful silos.

Existing networks between infectious disease researchers, both nationally and internationally, helped to bring multidisciplinary groups together during the COVID-19 response and allowed us to learn from other countries' experiences in real time. However, when networks are dependent on individuals and goodwill rather than established structures, they are vulnerable and can't be relied on for the future. Our whole genome sequencing capacity was rapidly ramped up and made important contributions to surveillance and response. This capacity needs to be firmly embedded in the public health system and sustained in the long term. Decisions on public health response were made with broad political and public support. The international experience shows how important it will be in future to ensure multipartisan political commitment to planning and public health, while continuing to maintain the political independence of disease control experts.

The effective responses of Māori and other communities to protect and support their own communities during lockdowns must be fully acknowledged.[2] In addition, holistic models of health and response that incorporate mātauranga Māori will help emphasise the interconnectivity between humans, animals and the environment. This increases awareness of conditions that allow outbreaks to emerge. It also reminds us that imported infectious diseases affecting livestock can also have substantial economic impact on our important primary industries, and potentially lead to the emergence of zoonotic pathogens that affect both animal and human health.

Transdisciplinary partnerships across animal, human and environmental health and with communities are essential approaches to combat infectious diseases and other health risks.[6] Understandably, we are currently focused on the fast pandemics that are the consequence of new, easily transmitted pathogens entering a susceptible human population. However, the impending pandemic of antimicrobial resistance will likely be slower to gain momentum but more progressive, sustained and harder to control. These challenges are further complicated by the currently weak response to the impacts of the climate crisis and ongoing ecosystem degradation. New Zealand does not have a good record for supporting transdisciplinary partnerships. Only last year a proposal for a collaborative Centre of Research Excellence focused on better preparing Aotearoa New Zealand for future infectious diseases risks was not funded.

The New Zealand Health and Disability System Review[7] and the New Zealand

Health Research Strategy 2017–2027[8] provide opportunities for better integration of science and research into the health system. A culture change is required to ensure research is central to the new health system, providing the science needed to inform policy, preparedness and best practice—critical for effective and agile responsiveness to future infectious diseases risks. The new Public Health Agency may provide a better platform for collaboration than the current arrangement. The latter has district health board-based public health practitioners and ESR-based surveillance experts, with a small communicable disease team and the Office of the Director of Public Health providing expertise in the Ministry of Health for both policymaking and some operational activities.

Research culture also needs to better accommodate applied research carried out in partnership with healthcare providers, communities, policymakers and government. A new generation of scientists and professionals is needed, driven by systems thinkers, who understand the policy- and decision-making processes, and are comfortable working with communities and multiple disciplines and across the science–policy interface. Valued for their breadth of knowledge and experience as much as their in-depth expertise, and working with humility across multiple stakeholder groups, these are the people who will help ensure past mistakes are not repeated.

Aotearoa New Zealand needs to build the capability and relationships that would comprise a transdisciplinary collaborative institution that includes the community, particularly Māori, and infectious disease experts including researchers, policymakers and disease control practitioners. This does not have to mean a 'bricks and mortar' institute but a structure that facilitates working together, with all partners deliberately learning from and informing each other's work (while maintaining political independence as appropriate). Some funding and staffing would be required to make this work. However, if we leave it to competitive research funding and the individual relationships of different groups and individuals, we will not have learned from this pandemic, and will not be doing the best for Aotearoa New Zealand.

As much as any other nation, we need to reflect on the report by the Independent Panel for Pandemic Preparedness and Response. We have done relatively well by global standards in our response to COVID-19, but the baseline is very low. We need to act now in order to learn from the current crisis and better prepare for the next one. Otherwise time, knowledge and momentum will be lost. As the report's summary states: "we have been warned."

Competing interests:
Nil.

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Improving the prescribing practice of junior doctors through interprofessional collaboration and evidence-based education

Dale Sheehan, Avril Lee, Arindam Basu, John Thwaites

The last decade (2010–2019) has seen calls to action to improve the prescribing practice of junior doctors.[1–3] An in-depth investigation into the causes of prescribing errors by foundation trainees in relation to their medical education (the EQUIP study[1]) in the UK reported a prescription error rate of 8.9% for all prescribed medicines, and although that is a UK study, there are similarities with New Zealand prevocational training programmes.[3] The EQUIP study revealed that existing teaching strategies are not working.[1] To believe a single intervention will prevent most prescribing errors is simplistic, and for improvement to occur, new prescribers need to learn from their mistakes.[3–5] Traditionally, the education of junior doctors has focused on their competence and professional registration requirements. Working in healthcare is collective and multidisciplinary, and errors occur through human and system factors.[6]

In response to similar calls to action in New Zealand,[1] the medical education units at two of the larger New Zealand district health boards (DHBs) began working on an education intervention to improve prescribing and medication safety. They explored ways to leverage the interprofessional collaboration between doctors and pharmacists in their everyday interactions to promote effective prescribing practice.[7] This early work encouraged pharmacists to work collaboratively with medical staff to integrate medication safety into the postgraduate year 1 (PGY1) programme using interprofessional teaching methods and role modelling collaborative practice.

In 2015, the intervention was expanded to include a role for pharmacists coaching PGY1s on the wards. The work was evaluated by recording prescribing errors and the feedback of PGY1s and educators. A significant improvement in prescribing was demonstrated, with qualitative results suggesting that pharmacists coaching PGY1s on the ward was the strongest intervention.[8]

Simultaneously, a programme in the UK known as 'ePPiFany' (Effective Prescribing Insight for the Future) was adopting similar strategies and achieving similar results.[9] Over the past five years, the UK and New Zealand teams have worked together to share strategies, outcomes and lessons learned, to contribute to knowledge about how workplace learning theory and interprofessional education improves the prescribing practice of junior doctors.

The UK ePPiFany approach

The ePiFFany educational approach is based on self-regulated learning and focuses on developing clinical reasoning when prescribing. It combines a simulated clinical encounter, which is filmed, with personalised and structured feedback, including a review of the filmed encounter, to facilitate deliberate practice throughout the four-month junior doctor rotation. A full description of the intervention is provided in Green, Shahzad and Wood.[9] The primary outcome measure, error rate per prescriber, was calculated using

daily prescribing data. The three-site ePiFFany case study demonstrated the impact of the intervention on improving clinical outcomes (ie, reducing prescribing error rates). The intervention improved prescribing and patient safety behaviour across different subspecialties and contexts.[9]

The New Zealand application of ePPiFany

Two New Zealand DHBs were offered the opportunity to pilot and adapt the evidence-based ePPiFany approach with the support of the UK team. The New Zealand team took a stronger focus on the role of the pharmacist as an interprofessional coach. Following the UK approach, the aim was to accelerate the prescribing performance of PGY1 doctors. We anticipated that, after three months of work experience, our intervention group would be performing at the same level that the control group would after 12 months of work experience and no intervention.

The programme aimed to accelerate the prescribing performance of PGY1 doctors. It was hoped that after three months the intervention cohort's prescribing would be at the level of performance as that achieved by the control group after 12 months.

Study design

The intervention was evaluated using a multi-method design with these objectives:

1. Assess the impact on patient care through reduced prescribing errors.
2. Facilitate quality improvement and programme development by documenting participants' experiences, insights and recommendations for improvement at each DHB site (PGY1 doctor, medical and pharmacy educators).

The first objective of this study was to assess the impact of a sustained educational intervention on prescribing practice over a three-month period. That intervention included simulations with personalised, structured, video-enhanced feedback and ongoing ward coaching by pharmacists on prescribing performance. Consistent with the intervention design used in Green et al (2020), an experimental group (consisting of PGY1s on their first placement) and an experienced control group (consisting of PGY1s on their fourth and final placement) was constructed to assess the effectiveness of the intervention. All prescriptions (pre- and post-intervention group) were audited daily and analysed for prescribing accuracy and appropriateness by an independent ward pharmacist.

In order to further programme development, qualitative data was also gathered through semi-structured interviews with PGY1 doctors and debrief meetings with medical and pharmacy educators to collect feedback about satisfaction, implementation, experience and sustainability.

Methods

Prescribing audit data collection and analysis

In following the UK model, the New Zealand pharmacists completed prescribing audits daily, recording prescribing errors by the PGY1 doctors for a six-month period. The first baseline data set at three months was collected from doctors on their final rotation (Quarter 4). The second data set was collected during the following three months, which was Quarter 1 for the new incoming PGY1 doctors who received the intervention (Figure 1). Data for Sundays and public holidays were collected on the next working day. Any gaps were identified and accounted for.

Data analysis

Error prevalence was calculated using the following formula:

Error prevalence = (Total number of errors / Total medicines prescribed) X 100

The error data were tabulated. The prevalence of errors was compared statistically on the basis of the test of proportions using R.[10]

Data was stratified by type of error, severity of error and grade of prescriber. The descriptions of numerator and denominator data and error severity are attached (Appendix Figure 1).

Figure 1: Audit data collection time frame.

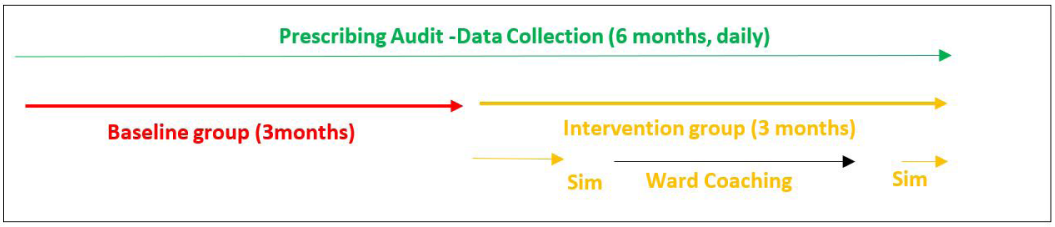

Table 1: The key components of the New Zealand intervention.

1.	Wards with an adult population and an average length of stay greater than three days and where PGY1s commonly prescribe (eg, general medicine and general surgery) were selected.
2.	Patients with complex but common conditions who had been recently discharged were invited to assist us with the simulations. Following information and consent, the patients' current notes and prescribing histories were used to develop a simplified set of notes for the simulations, and they were briefed on their role.
3.	The simulations reproduce a ward call where the PGY1s were asked to clerk three patients, review their medications, prescribe and present the patient to a consultant.*
4.	During the simulations, the PGY1 doctors were videoed taking a medication history. They then presented their findings in a mock handover to the medical specialist. The medical specialist and the pharmacist observed the simulation and determined the factors the pharmacist needed to coach on the ward (in the form of a written summary for the ward pharmacist coach) and provided some immediate feedback to the doctors. The simulation video was sent to the junior doctor to review, self-assess and use in their meetings with their pharmacist coach.
5.	A delayed debrief and guided self-assessment for the PGY1s by the pharmacist, using video recordings of the simulation, targeted the clinical reasoning for prescribing decisions. This generated learning goals for the doctor.
6.	Direct coaching from the pharmacist for complex prescribing tasks continued on the wards during the three-month rotation.
7.	A second simulation used the same patients who were briefed to disclose a deterioration of their clinical status that would require additional prescribing.
8.	Debrief of the PGY1s following the simulation focused on self-evaluation, exploration of clinical reasoning, identification of progress over the intervention period and setting prescribing learning goals for the next rotation.

*A full protocol of the simulation and the design of the ward coaching model is available on request from the corresponding author.

Qualitative data collection and analysis

PGY1 interviews

PGY1 doctors were interviewed individually using a semi-structured format (a mix of face-to-face and telephone interviews) within a month of the completion of the intervention by the independent project coordinator (Appendix Figure 2). Interviews were brief, pre-arranged and averaged 15 minutes, to ensure the doctors were not away from clinical service for any longer than necessary. Information sheets were shared at the time the interviews were arranged, and signed consent was obtained at the commencement of the interview. Responses were recorded on an anonymised template and checked for accuracy with the junior doctor at the end of the interview.

Medicine and pharmacy educator debriefs

Face-to-face group debriefs were held at each DHB site (site 1 and site 2) with pharmacists and medical education staff. Oral consent was obtained. Discussion focused on capturing each group's perception of the value of the project. They were asked: What worked well? What did not work well? Did you feel this was a good use of your time? What do we need to consider in the future? The facilitator took notes and sought clarification or elaboration of points that were unclear. Notes from sites were kept separate, as there were variations between site 1 and site 2. There was a focus on looking forward, programme improvement and future development, including other site implementations.

Data analysis

Initial thematic analysis was undertaken following Creswell's method.[11] Data from each stakeholder group were analysed for significant statements and quotes, and clusters of meaning were developed using colour coding. Common themes and patterns emerged from both sites and data from each site was combined. An informative label for each theme that resonated with the research team was selected.

Initially, feedback from medical and pharmacy teams was analysed separately. However, as significant site variations emerged alongside clear commonalities, medical and pharmacy responses were integrated for reporting results.

Ethics

This study received ethics approval from the UNITEC Research Ethics Committee (EC). EC registration number: 2016-1038.

Site approval and registration was awarded by DHB. On 21 June 2016 the New Zealand Health and Disability Ethics Committee formally deemed it to be outside their scope and that the study did not require their approval.

Results

Quantitative results: prescribing audit outcomes

There was a significant reduction of prescribing errors at both sites (Table 2).

The volume of prescribing on the wards at the two sites was comparable for the baseline and intervention groups (Table 2). Volumes were reduced at both sites for the intervention group due to the holiday period.

Junior doctor prescribing errors at both sites reduced remarkably following the intervention. At site 1 (DHB1), error prevalence reduced by about 79% (p=0.02). The error prevalence at site 2 (DHB2) reduced by about 38% (p=0.35).

Impact on the frequency and severity of prescribing errors

At site 1, the proportion of severe errors reduced by 100%, from 4.04 to zero, in the intervention group (Table 3). We did not have a significant impact on the severity of error at site 2 (Table 4).

Qualitative results

PGY1 doctor interviews

Interviews were conducted with 10 PGY1 doctors in total across the two sites with a 100% response rate.

Respondents were asked to rate their overall experience on a scale of 1 to 10, with 10 being the most positive. The median was 8 at site 1 (n=6) and 6.5 at site 2 (n=4).

Feedback was consistent for seven of the nine themes identified across the two sites

Table 2: Prescribing errors by site. Based on N=14 for DHB1 and N=17 for DHB2 control groups. In the intervention groups, N=6 for DHB 1 and N=4 for DHB2.

Baseline				**Intervention**				
DHB	# Overall prescribing volume	# Errors PGY1s	Error prevalence (%)	# Overall prescribing volume	# Errors PGY1s	Error prevalence (%)	% reduction in errors	p-value
DHB1	4,943	396	11.32	4,271	135	2.42	79%	0.02
DHB2	4,937	672	13	4,555	392	8	38%	0.35

Table 3: Site 1 error severity as a proportion of total errors prescribed (PGY1 data).

Severity	**Control** Items # 919 Prescribers #14 Errors # 104	**Intervention** Items # 620 Prescribers #6 Errors # 15	**p-value**
Minor	41%	13.3%	<0.001
Moderate	42.3%	80%	<0.001
Major	8.6%	0	<0.001
Severe	1.92%	0	0.002
Unknown	1.92%	6.6%	<0.001
Miscellaneous	4.26%	0	<0.001

Table 4: Site 2 error severity as a proportion of total errors prescribed (PGY1 data).

Severity	**Control** Items # 2181 Prescribers #17 Errors # 284	**Intervention** Items #898 Prescribers # 4 Errors #71	**p-value of proportions**
Minor	67.9%	69%	0.99
Moderate	31.3%	26.76%	0.58
Major	0.7%	1.4%	0.19
Severe	0	2.8%	< 0.001

and these consistent responses were all positive. The overall experience was valued by the PGY1s, who agreed that this training was most useful early in the training year; that their reasoning when prescribing was enhanced; and that they felt more confident. The authenticity of the simulation environment and use of real patients was helpful for learning. They valued all the feedback offered, but the video of the simulation appeared less useful than reviewing prescribing on the ward with the pharmacist. (Detail provided in Appendix Table 1).

Significantly, they all thought that the programme should be rolled out to a full cohort of PGY1s, and 60% thought it would be valuable to repeat the programme in their second postgraduate year, especially in subspecialty areas with complex medications (eg, gastroenterology, oncology).

Site variation emerged when the PGY1s were asked about improvements for the future.

Site variation themes

Information prior to consent ensured that respondents were aware this was a new programme and a trial, and that we wanted detailed comments on how to improve the programme for the next cohort. There were two areas of difference: the structure of the second simulation, and the experience of the delivery of the ward coaching.

Comments highlight variation in the implementation and delivery of the end-of-run simulation and the ward coaching across sites, which signals areas for improvement at site 2 and also considerations for the planning of new site implementations.

Medicine and pharmacy educators' debriefs

Both common and site-specific comments emerged that mirrored the PGY1 feedback. The educators all felt that it was worthwhile, supported the concept and wanted to continue to develop the programme in the future.

> *"Conceptually it's worthwhile."*
> *(Medicine educator, site 2)*

> *"We can see the benefit."*
> *(Pharmacy educator, site 1)*

Both sites reported positive responses from the PGY1 doctors, but both sites and both professions also noted the time and resources involved and felt that the current model would be difficult to sustain and deliver to a full cohort of 40–60 PGY1s.

There were several features to consider for the future before a full roll out could be undertaken. Comments highlighted variation between sites in preparation, ward culture and the pharmacists' previous experience and training as interprofessional coaches.

Differences between sites

1. Ward environment

Site 1 used a rehabilitation and general medical ward, and site 2 used a busy orthopaedic ward. Ward selection impacts on release time both to attend simulation and for meetings with the pharmacist.

> *"The wards that the intervention is based on need to be considered—for the very busy, acute wards, release time for simulation was hard."*
> *(Medicine educator, site 2)*

> *"Hard for pharmacists catching up with PGY1s when they are so busy."*
> *(Pharmacy educator, site 2)*

2. Simulation environment

Although simulations ran relatively smoothly, debriefs turned to a discussion of volume and capacity. At site 1 there was more technical help available from the simulation unit and more support staff were available to assist with patient support before and after the simulation. In addition, video recording and copying assistance ensured prompt return of the videos to the PGY1s. At site 2 there was less technical support.

> *"Using real patients is the gold standard but takes a lot of coordination, especially for the second simulation, to bring them in, support them and train them."*
> *(Medicine educator, site 2)*

> *"Need to use a full simulation unit with full support, which is resource intensive for large numbers of simulations. Could we run it* insitu *in ward linked to ward rounds?*
> *(Medicine educator, site 2)*

3. Engagement, training and briefing of pharmacists.

Engagement of the pharmacy staff early and training pharmacists for the ward-based

Table 5: Site variation PGY1s.

Theme	Site 1	Site 2
1. **Usefulness of the end of rotation simulation** At site 1, responses indicated the link between the two simulations was clear and that it enhanced self-assessment. Site 2 provided a less satisfactory experience.	I can see how the first and second simulation fitted together. I felt a lot more confident in the second simulation. I could see I had learned what to look for and find the info I needed.	Second simulation not useful felt it was being pushed in. Got most out of the first simulation. X was the best patient, as you not only used your real meds but also understood it was a simulation—understood the role. The other patient's not as focused—may have been unprepared.
2. **Coordination of pharmacy support and coaching** Although both sites valued the pharmacy input, comments varied across sites. One site was more coordinated and consistent in their ward coaching. We learned from both groups that meetings with pharmacists were best scheduled early (within the first week of the simulation) and ongoing meetings planned and structured around House Officer routines and work.	Talking with pharmacists in the week that followed about what happened in the session was very helpful. Practising on ward—the more you do the more you learn. Talking to team pharmacists was really helpful. Went through video and discussed the patients. But also met a number of other times on the ward, which was really helpful. Talked to pharmacist on the ward three times (about the simulation and cases), then informally every other day.	I can see that it is useful for pharmacy to be involved, but they need to get their timing right and understand the House Officer job better. An impromptu grab on the ward does not work—Here I have this thing (the video)—need to make a time and set it aside. The feedback in the ward was too limited. Met formally once with X. Feedback on my cases was all positive—not constructive and critical. More a pat on the back but what you want is a critical review. X said what I did well but it was too hard to remember—tried but meetings too late. Later sat down with Y for a longer session, but there was too much of a time delay even with the video—I could not recall my decision-making.

coaching is critical as there is a significant role shift for them, this varied by site. At site 2 the pharmacists were not as well prepared. Comments from this site by the pharmacists included:

> *"Our execution did not run as well as it could have."*
> *(Pharmacy educator, site 2)*

> *"Using our time is ok if they prescribe better."*
> *(Pharmacy educator, site 2)*

> *"Looking back, we needed to engage earlier."*
> *(Pharmacy educator, site 2)*

In comparison, site 1 had more experience working in a coaching role with junior medical staff and stronger pharmacy leadership. Their comments were:

> *"If it was rolled out to all PGY1s, it would decrease the pharmacist workload, as less follow-up would be needed."*
> *(Pharmacy educator, site 1)*

> *"It helped us build rapport—the PGY1s approached pharmacists more easily on other matters."*
> *(Pharmacy educator, site 1)*

> *"PGY1s would ring us with concerns."*
> *(Pharmacy educator, site 1)*

> *"Comments indicated a willingness for more pharmacy involvement in planning at site 1."*
> *(Pharmacy educator, site 1)*

> *"Communicate with pharmacists more before second simulation to have an idea of what the major issues or themes that pharmacists identified on the ward."*
> *(Pharmacy educator, site 1)*

The variation in pharmacist feedback across the two sites mirrors the PGY1 doctors' comments, highlighting the need for consistent training and preparation for all educators.

An incidental finding identified by the pharmacists at site 1 was that, during the simulation, six PGY1 doctors all prescribed differently for each patient.

Overall, the comments and discussion in all debrief groups can be summarised by this quote:

> *"A great educational opportunity—a good approach to teaching something so important, but we need to streamline it make it more efficient—resources are needed to back it."*
> *(Medicine educator, site 2)*

Limitations

Limitations due to small cohort size and site variation are acknowledged. Nonetheless, the outcomes do mirror the UK findings and demonstrate improvements in patient safety. As a trial, this project was about impact (measured by prescribing errors) and quality improvement, so was focused on transferability over generalisability. No two sites will ever be identical. The dual-site implementation highlighted regional strengths and weaknesses, raised key points for transferability of the programme to other sites and informed the project moving forward.

Discussion

Impact on patient outcomes

The results, which match the UK experience, demonstrate a significant difference in patient outcomes measured by prescribing error rate and error severity.[9] At site 1 we made a difference to patient outcomes beyond our expectation. At site 1 the error severity profile reduced significantly for three of the six categories while moderate errors increased.

We are unable to explain the increase in moderate errors. Clinical staff suggest that this finding may be connected to the timing of the first rotation in New Zealand. The first PGY1 rotation in New Zealand coincided with the summer holiday period and the start of a new rotation for many registrars. Lack of awareness of local protocols and lower staff volumes may impact communication. In addition, interpractitioner variability of prescribing, noted during the simulation, highlighted the importance of training PGY1 doctors in local protocols using current best practice and helping them to think critically about prescribing. The increase in moderate errors by prescribers new to a service highlights the need for effective training, given that consis-

tency in approach is a cornerstone of safe prescribing practice.

The Health and Disability Commissioner's analysis of complaints involving a medication error between 2009 and 2016 in New Zealand identified several factors that contributed to prescribing errors: failure to obtain necessary information (60%), failure to follow policy and protocol (20%), inadequate knowledge of the medication (17%) and training and orientation to the service (5% each).[12]

This supports our hypothesis that the availability of pharmacists at induction to support information gathering and improve familiarity with ward protocols and policies must be addressed early in the training year.

PGY1 doctor satisfaction

The training was well received by the PGY1 doctors. They not only found it useful but would like it repeated in their second year for more complex medication in subspecialties. From both patient care and the PGY1 doctors' perspectives, the evaluation shows that there is value in rolling out the programme to a full cohort at the trial sites, and that if a full nation rollout were undertaken, there is the potential for a dramatic impact on patient care.

Sustainability

On follow-up with the medical education units, medicine and pharmacy educators raised issues of resourcing and sustainability that cannot be ignored. Although this initiative demonstrated that the educational programme can make a significant difference to patient care, a key learning for the implementation team has been that the current model is extremely resource intensive, particularly during the simulation laboratory sessions, which take two hours per person and would be difficult to roll out to 40–60 interns.

Regional variation

A dual-site implementation reminds us that workplace contextual and cultural factors will vary across sites and any widespread implementation needs to anticipate this.

All sites have their own implementation strengths and challenges, and a national rollout would need to include flexibility to accommodate these differences. Regional variation and the preparedness of all professional groups is a key consideration. At site 1 the pharmacists had more experience and training for the coaching role, and this was evident in the feedback. Sites also vary with regard to levels of simulation support, ward staffing structures and the culture of wards, services and teams. These factors are important considerations for scaling up the project.

What next?

The model has several phases that draw on evidence-based educational practice, and it is now recognised that further work needs to be done to trial options for delivery at additional sites that would maintain these core principles. Two aspects are being explored:

1. Alternatives to running simulations off the ward at the beginning and end of the rotation. Two suggestions have emerged:
    - Doing small *in situ* simulations on the ward before or after ward rounds, with current patients and using iPhones to video the interaction.
    - Building scenarios into a workshop at the start of the rotation using pre-recorded simulations *in situ* or written cases. Use small group discussions to establish learning needs and as a baseline for self-assessments and self-directed learning at the end of the rotation.
2. Developing tips and training for pharmacists coaching junior doctors on the ward.

The combined feedback from this study, an earlier New Zealand study[8] and a study exploring pharmacy and medicine co-working in Australia[13] indicates that coaching pharmacists on the ward may be a key for successfully reducing prescribing errors. In our study, the preparation the pharmacists received prior to the pilot was more extensive at site 1 than at site 2, and site 1 pharmacists had more experience with coaching PGY1 doctors. A refinement for the future is to develop a consistent training programme for pharmacists with an interprofessional educator focus.

Towards a sustainable model for large cohort implementation

The ongoing goal is to develop a flexible and sustainable model to help train entire cohorts of PGY1 doctors. The key emergent theme from the New Zealand experience is the role of the hospital pharmacist in the training of PGY1 doctors.

At the start of the 2018/19 training year, site 1 trialled a version that drew on the ePiFFany experience but replaced the simulation with a pharmacist-led, case-based workshop as a precursor to the ward-based learning with pharmacist coaching. This appears to be a more sustainable model that combines the ePPiFany core principles of supported self-directed learning on the ward with pharmacist coaching, an initial workshop and targeted feedback. This will be implemented at site 2 for the 2020/21 training year. Both sites are providing this for all current PGY1 doctors with cohorts of 40 or more.

A process to monitor PGY1 doctors' improvements over the length of the attachment, and an activity to provide feedback at the end of placement simulation to align with the ePPiFany model's second simulation, is under development. The ongoing challenge is finding key indicators to measure improvements in medication safety during the training period that are more sustainable than an audit tool.

We hope that this refined model of delivery will have the flexibility to be shared with other New Zealand and Australian providers, and that we can work collaboratively to build and enhance the programme and share the ongoing development of resources.

Funding

Pfizer International funded the independent audit of prescribing that allowed us to include patient outcomes within the programme evaluation.

Appendix

Appendix Figure 1: Audit information.

Numerator data

The frequency of prescription errors, error type and error severity made by prescribers were collected by pharmacists across the six-month study period using a pharmacist-designed form. Criteria for grading the severity of errors were taken from standards used in the EQUIP study [3] (see below). All errors were coded by pharmacists, checked through a process of peer review and discussed with all clinicians in the project team.

The numbers of prescription errors were counted as the original prescription item and subsequent changes required per day.

Medicines administration to patients were checked electronically on the ePrescribing system for the number of doses given. The errors were manually entered by pharmacists into an Excel spreadsheet designed by the UK research team. All data was anonymised for analysis purposes.

Denominator data

The total number of medicines prescribed over the course of the study was collected weekly from the ePrescribing system, at the same time at the beginning of each week. The ePrescribing team and medication safety pharmacists collaborated to design a suitable way to extract this data. This enabled the number of errors to be calculated as a percentage of the total number of medicines prescribed.

Assigned error severity and associated probability:

Error severity	Associated probability of harm
Minor	0.1
Significant	0.4
Serious	0.6
Severe	0.9

Appendix Figure 2: Semi-structured interview questions—PGY1 doctors.

1. Please rank your overall experience within this three-month experience from 1–10 (10 being highest)?
2. Was the simulation helpful as an orientation to this ward/service?
3. What helped and what hindered your learning regarding prescribing on this placement?
4. What activities supported you in your prescribing practice on this ward?
5. Any suggestions for the future?

Appendix Table 1: Site consistent themes PGY1 interview data

Site consistent themes	Quotes	Comment
Overall, the experience was valued	"At first did not know the best treatment now feel more sure." "Basics covered med school, but interactions not emphasised as much."	Universally both House Officer cohorts found the experience positive and all stated that their thinking around prescribing had improved. Significantly, they all thought that the programme should be rolled out to all HOs and 60% thought it would be of value repeated in their second postgraduate year in subspecialty areas (eg, gastroenterology, oncology).
Timing	"Simulation best early in the year and at the start of the run." "Useful on the first run - exposed to situations not seen yet. Was food for thought - when you saw them in clinical you knew how to think through the situation?"	This experience is most useful early in the intern year and at the start of the rotation.
Enhanced awareness of the thinking that surrounds prescribing	"Enhanced my thinking through prescribing and cases gave you a chance to think and discuss medication decision." "I think better about it now - highlighted how I should be thinking about prescribing at each step."	At the end all House Officers on both sites reported being more aware of what they should be thinking about when prescribing
Nature of feedback	"Used video but it was not as helpful as looking at the list of the choices I made on the day. We went back to that – it was more helpful than the video." "Looked at video (did not like that). I asked to look at the list of what others had done and that got me thinking about other options. Talked about what I could do better."	HOs were not convinced the video was needed (80%) but written feedback immediately after the simulation was valued.
Simulations assisted learning	"Scenarios were helpful as I had not encountered all the medications before." "You are taught to do a full med history at medical school but changes when you start work you have less time. So it was good to do this early without consequences."	Authentic simulation environments, real patients and their medications and conditions similar to 'work' support learning

HO = PGY1 doctor

Competing interests:
Nil.
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What helps and hinders metformin adherence and persistence? A qualitative study exploring the views of people with type 2 diabetes

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ABSTRACT

AIM: To explore the views of people with type 2 diabetes who had initiated metformin monotherapy about what influences adherence and persistence.

METHODS: We recruited participants through primary care, using purposive sampling, and undertook face-to-face, audio-recorded, semi-structured interviews with 10 Māori, 10 Pacific, and 10 non-Māori non-Pacific patients who had started metformin monotherapy for type 2 diabetes within the previous two years. A thematic analysis was undertaken using the Theory of Planned Behaviour as the overall theoretical framework.

RESULTS: The perceived benefits of taking metformin included improving glycaemic control, preventing or slowing the progression of type 2 diabetes, and avoiding serious complications. Side effects (predominantly gastrointestinal) were the most commonly cited disadvantage. Participants employed a variety of strategies to help them take metformin regularly. Key reasons for initial sub-optimal adherence and persistence were side effects and not accepting the diagnosis of type 2 diabetes. Subsequently, omitting to take tablets was commonly unintentional (due to 'forgetfulness'). For many Pacific participants, changes in routine related to community and church events, or shift work, contributed to sub-optimal adherence. Some Māori participants would have preferred to use traditional medicines.

CONCLUSION: We identified a number of factors within the scope of healthcare services that may assist healthcare providers to focus on, and address, some of the issues that appear to be of primary importance to people when they are prescribed metformin.

Type 2 diabetes is a major public health issue globally and in New Zealand.[1–5] Findings from the 2018/2019 New Zealand Health Survey suggest that 6.4% of the overall New Zealand population aged >25 years has diagnosed type 2 diabetes,[2] and data from the Virtual Diabetes Register reveal that the number of people with diabetes of any type (the majority of whom would have had type 2 diabetes) increased each year between 2010 and 2019.[3] There are significant inequities in type 2 diabetes prevalence in New Zealand, and Māori, Pacific, and low-income groups are particularly affected.[2,4,5]

Metformin monotherapy has been recommended as the first line pharmacological therapy for type 2 diabetes in New Zealand,[6–8] which is in line with guidelines and consensus statements from the UK National Institute for Health and Care Excellence,[9] the Scottish Intercollegiate Guidelines Network,[10] the European Association for the Study of Diabetes,[11] and the American Diabetes Association.[11]

Internationally, qualitative studies have examined factors that influence adherence to oral hypoglycaemic agents.[12–28] However, only one[28] of these studies focussed specifically on metformin and very few explored

patients' perspectives on barriers to, and enablers of, adherence in the period following initiation of oral hypoglycaemic therapy—a time that may be the most critical for establishing regular use of the drug. No similar studies have been undertaken in New Zealand. We therefore carried out a qualitative study to explore the views of Māori, Pacific, and non-Māori non-Pacific patients with type 2 diabetes about what helps and hinders metformin adherence and persistence after initiating therapy.

Methods

Theoretical framework

The Theory of Planned Behaviour was used as a theoretical framework to explore factors that influence metformin adherence and persistence within the New Zealand context. This theory asserts that the intention of a person to adopt a certain behaviour (eg, medication adherence) is determined by three important constructs:[29]

i. *Attitude toward the behaviour* (eg, perceived advantages and disadvantages of medication adherence)
ii. *Subjective norm* (eg, perceived social pressure regarding medication adherence or non-adherence)
iii. *Perceived behavioural control* (eg, perceived factors that impede or facilitate medication adherence)

Interviews with Māori and Pacific participants were further framed by Te Whare Tapa Whā and the Fonofale model, respectively.[30,31]

Eligibility criteria

Because a recent quantitative study undertaken by our group revealed a drop in adherence and persistence that was particularly marked in the first two years following initiation of metformin monotherapy,[32] we opted to interview people within that two-year period in order to maximise the likelihood that any participants who had not taken metformin as prescribed would still remember what had contributed to sub-optimal adherence or discontinuation. Therefore, to be eligible for inclusion in the study, potential participants needed to have been prescribed metformin monotherapy for type 2 diabetes for the first time within the last two years. Members of this group were eligible for inclusion regardless of their current treatment status (ie, still using metformin monotherapy, using another antidiabetic pharmacological regimen, or not using any antidiabetic pharmacological regimen); we did not exclude people who had discontinued pharmacological treatment or changed regimens, as they may have had different experiences in relation to metformin adherence than those who continued, and it was important to capture that information. In addition, potential participants needed to be at least 18 years of age, able to converse in English, and willing and able to give informed consent.

Recruitment

Recruitment took place through primary care providers in Auckland, Wellington, and Dunedin. The providers included mainstream general practices; a healthcare provider for Māori, Pacific, and low-income families, as well as others who experience barriers to primary care; a Māori primary health organisation; and a Pacific healthcare provider. Practice staff generated a list of potentially eligible participants, along with a minimal set of variables (age, gender, self-identified ethnicity, and concomitant health issues), and used this list to take a purposive sample to facilitate the recruitment of a diverse group of participants. They then sent a letter of invitation and information sheet to the selected patients on our behalf. Recipients of the letter were invited to contact us if they were interested in taking part in the study, or if they required any further information before making a decision about participation. Arrangements were made for a face-to-face interview with each eligible participant at a time and place that suited them. *A priori* we proposed to recruit a total of 30 people—10 Māori, 10 Pacific, and 10 non-Māori non-Pacific.

Interview

Participants took part in one semi-structured, face-to-face interview between June 2018 and April 2019 about type 2 diabetes and their use of metformin. While guided by the Theory of Planned Behaviour, the interviewer asked open-ended questions and allowed for more in-depth enquiries to be made depending on the answers to those questions. An interview guide (see Appendix Table 1), which contained a list of questions and topic areas to be covered,

was developed by the research team. A draft version of the guide was discussed with the project's advisory group and was refined before being used during interviews with study participants. Written consent was obtained by interviewers prior to starting an interview. The interviews varied in duration, with most lasting between 30 and 60 minutes. Following the interview, participants were offered a $40 supermarket voucher as koha.

All interviews were audio-recorded with the permission of the participants, except for two: during one there was a technical problem with the digital recorder, and one participant preferred not to be recorded (comprehensive notes, including verbatim quotes, were taken during both of these interviews). Field notes were taken alongside the audio-recordings. Interviews with Māori participants were mostly undertaken by a Māori member of the research team and interviews with Pacific participants were undertaken by two different Pacific interviewers (one Samoan and one Tongan). Kaupapa Māori and talanoa research approaches were used in interviews with Māori and Pacific participants, respectively.[33,34]

Transcription of interview audio-files

The recorded interviews were transcribed by a professional transcription service. Each interviewer checked and corrected, if required, the transcripts of the interviews they had conducted, removed all potentially identifying information, and added any necessary explanatory notes. In addition, to minimise the potential for error, one researcher independently listened to all the audio-files and made corrections to the transcripts if required.

Analysis

Checked transcripts were uploaded to NVivo version 12 (QSR International, Victoria, Australia) to assist with data organisation and analysis. After six interviews had been completed and transcribed (two each with Māori, Pacific, and non-Māori non-Pacific participants), three members of the research team undertook a preliminary thematic analysis, using the Theory of Planned Behaviour as the overall theoretical framework. The researchers read the six transcripts to familiarise themselves with the data, independently coded themes using a loose coding framework and then met to discuss their provisional coding. Once a consensus on themes and sub-themes was reached, a coding dictionary was developed. The dictionary was used to refine the coding already undertaken and to code subsequent interviews; additional themes were added to the coding dictionary as they were identified. To promote consistency of coding, half the interviews were double-coded. To facilitate an overview of the data, one investigator coded all the interviews, cross-checked against the coding undertaken by other members of the research team, and then selected relevant quotes to illustrate the key themes. The results of this analysis were then circulated to the other members of the research team to be discussed and confirmed. Feedback discussion sessions were also held with participants.

Ethical approval

The study was approved by the University of Otago Human Ethics Committee (Health) (reference H18/058).

Results

Characteristics of participants

The characteristics of the 30 participants are shown in Table 1. We interviewed 10 Māori, 10 Pacific, and 10 non-Māori non-Pacific participants across a broad age range; 22 participants were women. Most participants were taking metformin monotherapy when they were interviewed; some participants had escalated to more intensive treatment or had switched to another oral hypoglycaemic; and a few participants were not taking any antidiabetic agents—for some this was intentional and for others it was because their supply had run out.

Perceived advantages and disadvantages of taking metformin

Initial and subsequent feelings about taking metformin

Typically, metformin was first prescribed at the same time that type 2 diabetes was diagnosed and participants reported a diverse range of feelings about starting the drug, including denial about the diagnosis of type 2 diabetes and the need for treatment, a general reluctance to take any kind of

Table 1: Characteristics of study participants.

Characteristic	Number (n=30)
Age category (years)	
35–39	2
40–44	1
45–49	3
50–54	4
55–59	8
60–64	5
65–69	4
70–74	2
75–79	1
Gender	
Female	22
Male	8
Ethnicity	
Māori	10
Pacific	10
Cook Island Māori	1
Samoan	3
Tongan	3
Niuean	1
Fijian Indian	1
Tuvaluan	1
Non-Māori non-Pacific	10
Treatment regimen at time of interview	
Metformin monotherapy	23
Metformin + gliclazide	1
Metformin + gliclazide + insulin	1
Gliclazide monotherapy	1
None*	4

*One participant had discontinued metformin monotherapy because of reported improvements in glycaemic control following major changes to diet and physical activity levels; one had discontinued because of severe diarrhoea; two had run out of metformin and had not returned to their healthcare provider to obtain a new prescription.

medication, feeling they had no choice, disappointment that lifestyle changes had been insufficient to improve glycaemic control, that it was a 'wake-up call' about the seriousness of type 2 diabetes, relief that insulin was not required, and a willingness to see whether metformin improved glycaemic control and prevented serious complications.

By the time of the interview, the views of most of those who were initially unhappy about starting metformin had shifted in a positive direction. There appeared to be several explanations for this shift. A few people commented that, although it had taken time, they had come to accept the diagnosis of type 2 diabetes. For some, observing that metformin had improved glycaemic control had played an important role. Other explanations included developing a better understanding of the benefits of taking metformin, finding that any initial side effects spontaneously resolved, developing strategies to mitigate any side effects, incorporating taking metformin into the routines of daily life, and realising that it was still possible to lead a full life while taking metformin.

Perceived benefits of taking metformin

Participants had several responses when asked about the benefits of taking metformin (Table 2). Glycaemic control was the most frequently cited benefit, followed by prevention of long-term complications of type 2 diabetes such as loss of eyesight, loss of limbs, and renal failure requiring dialysis. Prevention of coronary events and stroke was not mentioned.

Things participants disliked about taking metformin

The most commonly discussed negative aspect of taking metformin was the side effects, predominantly gastrointestinal (Table 3). In some instances, the gastrointestinal disturbances were reasonably mild and short lived, although in others they were severe and had a substantial impact on life and work. Participants with severe symptoms often reduced the dose of metformin (either on the advice of their doctor or of their own volition) or changed the time(s) they took metformin, and some stopped taking metformin altogether (either temporarily or longer term).

Perceived views of others about participant taking metformin

Participants identified various people, in addition to their healthcare providers, who approved of them taking metformin, including their partner, other family members, and friends. Conversely, a few participants felt their partners, other family members, or friends disapproved of metformin use. However, these participants reported that the opinions of others did not prevent them from taking metformin, because they felt it was helping them or they were not convinced by proposed alternative approaches.

Perceived facilitators of, and barriers to, taking metformin

Factors that helped participants to take metformin regularly

A key motivation for participants trying to take metformin as prescribed was the desire to remain well for both themselves and their families. Participants also reported a variety of strategies that helped them take metformin regularly (Table 4). Partners, other family members, friends, and work colleagues also played an important role for some participants, but some did not discuss their type 2 diabetes with others or were emphatic that it was their own and no-one else's responsibility to remember to take metformin.

Good relationships with healthcare providers also facilitated use of metformin. Some participants spoke of the importance of 'being known' by their healthcare providers, being able to talk easily, recognising that their healthcare providers genuinely cared about them, appreciating 'straight talking', being able to ask questions, feeling they could relate to their healthcare providers, and generally trusting their healthcare providers to give them the appropriate treatment and advice. Some Māori and Pacific participants also highlighted the importance of having Māori and Pacific healthcare providers who shared their cultural identity and language.

Factors that made it difficult to take metformin regularly

The majority of participants reported they had sometimes missed taking their metformin tablet(s) at the usual time; for

Table 2: Perceived benefits of taking metformin.

Perceived benefits	Illustrative quotes
Improves glycaemic control	I guess it stabilises my blood sugar... because the last time I had my blood test it was 71. And I went down last week [to the medical centre], it was 64. So I guess that's a bonus. I guess I can see the big change of taking the metformin, you know. *[Pacific participant, female]*
Reduces risk of complications of type 2 diabetes	The only thing with the diabetes, it's worth controlling 'cause of losing limbs and eyesight. That's the only thing that worries me. [Māori participant, female] Yeah but I also noticed different types of suffering in my aunties and my father and my uncles went through. Um... some of them lasted up to 80 but there's no problem, they never take, they weren't on insulin or anything. And I thought to myself I want to be like them and be, listen to the doctor and get... Some of them were on insulin very fast and they had bad kidneys and they have um... ...dialysis. So I don't want dialysis. *[Pacific participant, female]* ...and I s'pose it worries me a little bit that... the higher risk of infection and things like that because of diabetes, so… probably what keeps me on the metformin better. *[Non-Māori non-Pacific participant, female]* ...so I see the pills as the reason why I'm not in the ground... and I want to be around to enjoy whatever time, you know, in this world you have... But I know that it does, like I said, it's like putting money in the bank. I know that it's going to keep me here a bit longer. I know that if I went dead cold turkey, my diabetes would come back and I'd be stuffed. [Non-Māori non-Pacific participant, male]
Prevents or slows progression of type 2 diabetes and subsequent need for insulin	I mean I think metformin's a good thing as long as it... you know, it works to make sure that it keeps you off from getting any worse so that it makes you end up going onto the insulin side of things. And if that's what it does and that's what it is, keeps preventing you from getting worse to that stage, then it's all good to me. And there's no way I ever want to get to that stage. *[Non-Māori non-Pacific participant, female]*
Reverses progression of type 2 diabetes	I've been now described officially as pre-pre-diabetic, after a year of working on things. My HbA1c when I was first was diagnosed was 102. Then after… six months, I think, it was cut back to 48. And then the last two readings, I can't remember when they were done… one was just done recently, were both 40, which is pre-diabetic. But I mean that doesn't mean it's the end of the battle, I keep making the changes. *[Non-Māori non-Pacific participant, male]*
Helps with weight loss	But it has helped me to lose the weight... *[Non-Māori non-Pacific participant, female]*
Controls symptoms	Um, well it helps me in the fact that I don't feel the cold and the other sort of symptoms that come around diabetes that I used to. I must say that this morning, for the first time in a long long time, that I can remember, I didn't have to get up in the night to go to the toilet, which is a big change. [Non-Māori non-Pacific participant, male] ...it gives me more energy. *[Māori participant, female]* I know I'll be dizzy if I don't take my medication. *[Pacific participant, female]*
Provides reassurance that there is something that helps to control type 2 diabetes	Definitely it's the thought, it's the reassurance, that I've got this that's helping me inside my body. You know? *[Pacific participant, female]*
Has broader health benefits	I saw something on [TV programme] about metformin being the miracle drug. There's a big study in the States and they wanna know why they don't release metformin as a drug to take to help with your health, maintain your health. *[Māori participant, female]*

some, this had happened very occasionally, whereas for others it had occurred more frequently. Almost all of these participants had been prescribed metformin twice daily and many mentioned they were more likely to miss their evening dose. A change in routine was the most common factor that made it difficult to take metformin as prescribed (Table 5).

Although no participants identified people who intentionally made it difficult for them to take metformin regularly, a few commented that short appointment times made it difficult to establish a relationship with their general practitioners, and another questioned whether doctors really understood what it was like to take the medications they prescribed. A couple of participants also noted that the absence of active support from their partners or other family members made it harder to take metformin than it otherwise might have been.

Sources of help for metformin-related issues

The most commonly cited sources of help for metformin-related issues were the Internet, general practitioners, and nurses. Importantly, many of the people who mentioned the Internet appeared to undertake broad undirected searches, and not all participants had access to a computer or smart phone.

Table 3: Things participants disliked about taking metformin.

Things disliked	Illustrative quotes
Side effects	...the bowel situation was horrendous... For the first couple of months, I very rarely went out because I was too scared to be far away from the toilet. I think it was a case of 'I could have coughed and had an accident'... But after the first couple of months, it started to go away or settle down and I thought I could deal with it. There were still times when it happened, but not as much. And then when I decided to… adjust or, yeah, adjust my medications to suit myself, it worked better... So instead of taking morning and night, I take two tablets first thing in the morning… *[Māori participant, female]* The first time I took it, after about two days, I felt quite nauseated and was dry retching. So I looked up Dr Google. And I saw nausea can be that, so I just halved it. And I took two days on half a tablet and they said the symptoms would settle. And I went back up to the full one and it was fine. *[Non-Māori non-Pacific participant, female]* All of a sudden I just went off food and I just couldn't stand this. Maybe my taste buds, it's just something was happening, you know and I thought 'ok, give that a miss...' *[Māori participant, female]*
More pills to take	Then the metformin came along and then, you know, increase the metformin and then you're taking five. And then next minute, you're taking six. And then that's in the morning and you have to take three or four in the evening. That's a real burden to me. *[Pacific participant, female]*
Taking any sort of medication	I'm not a pill taker 'cause I've never been a pill taker. I fight even to take a Panadol. *[Non-Māori non-Pacific participant, female]*
Being questioned by others about taking metformin	They [participant's children] don't ask questions now. Like before they asked, 'what's that for'? Or, you know, it really upsets my feelings. *[Pacific participant, female]*
Being reliant on medication and anxiety about running out	If I had an alternative, I wouldn't be taking it. That's just how I see it... It's just like I'm controlled by this drug now… I get sort of worried when there could be a natural disaster, as such, and I haven't got enough stock. That will be it. And that sort of plays on my mind a little when I know that I'm running out of stuff. So I'll have to, you know, go and get some more. *[Māori participant, female]*
Impact on family and social life	It did at the start... with... because of the pricking all the time. But now, because it's under control, it is easier. *[Non-Māori non-Pacific participant, female]*

Discussion

Overview

This study has identified factors that help and hinder adherence to metformin in the critical period following initiation from the perspectives of Māori, Pacific, and non-Māori non-Pacific people with type 2 diabetes in New Zealand. Together, the themes identified from the participants' accounts have provided a context for considering the sub-optimal adherence and persistence observed in our national quantitative study.[32]

Findings in relation to previous research

Consistent with qualitative research elsewhere, we found that the development of an understanding of type 2 diabetes, and the important role that medication plays in its management, was a dynamic process that occurred at differing speeds for different individuals,[14,18,26] and that delays in accepting the diagnosis had a negative effect on initial adherence and persistence.[14,15]

Our findings relating to the perceived advantages and disadvantages of taking metformin are broadly in line with the findings of qualitative explorations undertaken in diverse settings (eg, Scotland,[26] Brazil,[12] Canada,[13,19] the United States,[28] Malaysia,[20] among Nepalese living in Australia or Nepal,[21] and Turkish immigrants in Belgium[22]), although only one[28] of those studies focussed solely on metformin.

The responses of our participants raise two important points. First, it is interesting that the long-term complications of type 2 diabetes they cited were retinopathy, lower-limb amputation, and end-stage renal disease, but coronary heart disease and stroke were not mentioned. This suggests either a lack of awareness that atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality among people with type 2 diabetes,[35] or

Table 4: Strategies participants used to help them take metformin regularly.

Strategies	Illustrative quotes
Establishing a routine	…in the morning, I take this, brush my teeth, have my medication. At night, brush my teeth, have my medication, the end. So, I don't forget. *[Māori participant, female]*
Carrying supply of metformin tablets	Yeah, it's [pill container] in my handbag [all the time]. Yeah. And I make sure to fill it up when I'm going away. *[Māori participant, female]*
Using a pill dispenser	I set my meds up for the week and I have them in different coloured containers… yellow canister for the morning ones, purple for the night. *[Māori participant, female]*
Keeping metformin in a place where it will be seen	I just have it over on that bench, so when I get up to make a cup of tea... I see it there. *[Māori participant, female]*
Using pharmacist-prepared blister packs	'Cause I kept, kept forgetting. That's how I ended up in A&E. So they put me on these [blister packs] with days of the week. *[Māori participant, female]*
Keeping a supply of metformin at work	I have... um... my... here at work, I have a bottle here. *[Non-Māori non-Pacific participant, female]*
Keeping an extra supply of metformin at home	'Cause I always have at least another month's supply in my drawer… 'Cause I got caught out once. I will never get caught out again. *[Māori participant, female]*
Adapting prescribed frequency	When I used to take my one in the lunchtime, they would say 'have you taken your medication?' No, forgot. So I changed it, just take it in the evenings and the mornings. *[Pacific participant, female]*
Keeping a notebook	I've got one of those wee notebooks where I write all the blood sugars and just note when I take them, the times. *[Non-non-Pacific participant, male]*
Prioritising self	...I'm at the stage where 'no, it's about me', you know. And I think that's it. 'It's about me now, and this is what I need to do to make me well.' *[Māori participant, female]*

Table 5: Factors that made it difficult to take metformin regularly.

Factors that made it difficult	Illustrative quotes
Being away from home	…or if I'm on holiday, I tend to forget the morning one. *[Non-Māori non-Pacific participant, female]*
Changing time zones	'Cause I was mucking them up and some days I was completely forgetting them for days on end. 'Cause you were travelling for 24 hours and you'd think you had them. Couldn't remember if I had it the day before or the day before that, and... *[Non-Māori non-Pacific participant, male]*
Unexpected events	If, like say, I got to work and all of a sudden we're asked to be somewhere or go somewhere, like that's an example of when I keep missing it because I haven't planned to take it with me *[Pacific participant, female]*
Changes in meal times	Taking medication in the evening is kind of different because I may eat dinner at different times so it is highly likely I may forget, but not too often. *[Pacific participant, male]*
Eating out	Thursday night, usually when I go out for a meal, that's the only night I miss out. *[Non-Māori non-Pacific participant, male]*
Being very busy	…but I will have some days where 'oh [exclamation], I forgot to take it this morning' because I've been rushing around doing something else… *[Non-Māori non-Pacific participant, male]*
Having no time for oneself	I am managing my tablets now, but it's taken me a wee while to get to a… to get to where... um, there's time, there's time for me. *[Māori participant, female]*
Putting others first	I probably follow like most Polynesians or Māori and we just don't… we care, but not... I dunno, we care about others, rather than caring about yourself. And so as long as my kids are ok, husband's ok, the dog's ok, then things are ok. But it's actually… yeah, not really. *[Māori participant, female]*
Tiredness	Sometimes I forget. When I'm tired… Sit down and relax and I go to sleep. *[Māori participant, female]*
Memory issues	…because my memory is like a sieve now. 'Cause, I'll be honest, probably in a couple of hours, I will have forgotten everything we talked about. *[Māori participant, female]*
Having to take metformin with food	It started off metformin just at night... and then a wee while ago, she [doctor] said, 'oh I'd like you to start having one in the morning'. That's my problem one. It's a problem for me because I've spent 50 years being a smoker and my breakfast has been coffee and a fag… So when I find out that these pills I've gotta have with food, it's like oh... and I'm gagging because I, sometimes I can't get up early in the morning and have food, it's just not… I don't know whether it's a mentality thing or whether it's just what it is. But I've really struggled. So sometimes at the beginning, I wasn't taking the pill because I wasn't having food... *[Non-Māori non-Pacific participant, female]*
Other timing issues	It's taken me a while to... you know, [find] the right times to have it. You know, like I started having it at eight o'clock in the morning and eight o'clock at night. Um, but then, I started forgetting. But now because I drop my daughter off at her work bus at the station down here, um at four o'clock in the morning. So I've decided that's the time I'm going to take it. So four in the morning, and, and maybe four in the afternoon… And that's working out quite nicely for me. *[Māori participant, female]*
Cost	I don't see the Dr because I have to pay. *[Pacific participant, female]*
Other health conditions more important than type 2 diabetes	So I've got more metformin pills than I've got my blood pressure. Which shows me that I'm not taking all of my metformin… 'Cause in my head, the heart's more important than the kidney. *[Māori participant, female]*

that losing sight, a limb, or kidney function was of greater importance. Second, some researchers have expressed concerns about beliefs (as were held by some of our participants) that taking oral hypoglycaemic agents as prescribed will prevent the progression of type 2 diabetes and obviate the need for treatment escalation.[13] They argue that, while such beliefs may have a positive impact on adherence, the disadvantage is that adherent patients will experience a sense of failure, or may feel that the medication 'doesn't work', when the natural progression of the disease requires intensification of therapy, and this may have a detrimental impact on adherence to future treatment regimens.

The approaches that participants employed to help them take metformin are all consistent with strategies reported in qualitative studies internationally.[12,13,21,22,26] Comments made by the participants also highlighted the importance of establishing and maintaining good patient–healthcare provider relationships and tailoring communication styles to the preferences of patients. In contrast to some international studies,[13,22] a lack of confidence in doctors' expertise appeared to be very uncommon.

Our findings in relation to barriers to adherence and persistence are congruent with international findings.[12,13,20–22,24,26] Missing a metformin dose was most often unintentional (due to 'forgetfulness') and was more likely to occur when there was a change in routine. As others have noted,[18,22,26,27] forgetfulness is a particular issue for people prescribed oral hypoglycaemic drugs for type 2 diabetes because there are usually no symptoms to remind patients to take their medication and no reduction of symptoms to positively reinforce adherence.

The cost of visiting a doctor and prescription charges were issues for some participants. This is in line with the findings of the 2018/2019 New Zealand Health Survey, where cost was a barrier to visiting a general practitioner for a medical problem in the preceding 12 months for 13.4% of all those interviewed, and where 5.3% reported that they had not filled a prescription because of cost.[2] The corresponding proportions were higher among Māori, Pacific peoples, and those living in the most socioeconomically deprived areas.

Qualitative research in other settings (American Samoa,[23] Malaysia,[20] Ghana[24] and among Nepalese living in Australia or Nepal,[21] Turkish immigrants in Belgium[22] and British Indian and Pakistani patients living in Scotland[17]) has found that cultural and religious beliefs and obligations influence type 2 diabetes medication adherence (sometimes positively and sometimes negatively), and in New Zealand a preference for traditional Māori medicines over 'Western' pharmaceutical therapies emerged as a theme in a qualitative study that explored perceived barriers to glycaemic control among 15 people (Māori, Fijian, New Zealand European) with type 2 diabetes who were attending a diabetes clinic.[36] In our study, some Māori participants said they would have preferred to use traditional Māori medicines rather than metformin, and a few Pacific participants talked about sometimes forgetting to take metformin when they were busy with community and church events. One Pacific participant alluded to religious beliefs leading to sub-optimal medication adherence in his community, although religion did not appear to have influenced adherence among the participants we interviewed.

The main sources of help for metformin-related issues that participants cited were healthcare providers and the Internet, which is consistent with the findings of a New Zealand survey of public knowledge, and desire for knowledge, about medicine safety issues.[37] It is notable that many of the participants who used the Internet for information about metformin undertook general untargeted searches, and only a few appeared to consider the trustworthiness of the sites they visited. In addition, not all participants had Internet access. These findings are consistent with previous reports that have revealed low levels of health literacy in New Zealand[38] and reinforce initiatives introduced to help the New Zealand health system contribute to building health literacy.[39] They also highlight the need to provide patients with resources through a variety of channels, as it cannot be assumed that online resources will suit everyone.

The authors of a meta-synthesis of qualitative studies that explored self-management of type 2 diabetes have cautioned

against a simplistic emphasis on the role of the individual in managing their disease, as such an emphasis downplays the role of broader influences and determinants of health.[40] Similarly, researchers in New Zealand have highlighted the steps, each with its own complex set of determinants, required for an individual to obtain a prescription medicine.[41] It follows that there is a balance to be achieved between encouraging self-efficacy and self-management of type 2 diabetes and recognising the complex cultural, social, economic, geographic, and political environments in which individuals live. An unintended consequence of focussing entirely on self-management without addressing broader systemic factors is that it might foster counterproductive guilt and shame if self-management appears to have 'failed'. This delicate balance was illustrated in our study with some participants vigorously asserting that they were responsible for managing their type 2 diabetes and feeling empowered to make positive changes in their lives, while others appeared to be grappling with a heavy burden of self-recrimination for having diabetes and/or sub-optimal glycaemic control, feelings that sometimes prevented them from visiting their healthcare providers. Similar feelings of guilt and shame have also emerged in other New Zealand[36,42] and international[16,26] qualitative studies involving people with type 2 diabetes. An added complexity, observed in our study as well as in other qualitative studies of diabetes in New Zealand[36,42] and elsewhere,[26] is the common lack of understanding that type 2 diabetes is a progressive disease and that a need to escalate treatment is not synonymous with personal failure on the part of people with the disease.

Strengths and limitations of the research

This study is the first New Zealand-based qualitative investigation of the views and experiences of people who initiated the recommended first-line therapy, metformin monotherapy, to treat type 2 diabetes.
The study has several strengths. First, we included equal numbers of Māori, Pacific, and non-Māori non-Pacific participants to ensure that the views of Māori and Pacific patients were equally represented alongside those of non-Māori non-Pacific patients.

Second, we took an active recruitment approach and sent personal invitations to potential participants via primary care, as this increased the likelihood of recruiting a broader range of participants than the highly selected group of people who are likely to respond to a generic public advertisement (and who are likely to have better adherence). Recruitment in three cities, through mainstream general practices as well as services for Māori, Pacific, and low-income families, also contributed to ethnic, socioeconomic, and geographical diversity. A further advantage of our recruitment method is that we were able to reassure potential participants that we were not involved in the process of identifying potentially eligible patients and therefore did not have access to their personal healthcare data and, conversely, healthcare providers did not know who had agreed to take part in the study. This may have helped to encourage open discussion.

Third, to further facilitate free discussion, interviews were conducted at a time and place of each participant's choosing; family members or other household members were present if invited by participants; and there was congruence between the ethnicity of participants and interviewers. We used an established theoretical framework to develop the interview guide, but also took a flexible approach that allowed the participants to tell their stories in their own way.

Fourth, several steps were taken to check the accuracy of the interview transcripts. Similarly, the coding dictionary was developed through consensus and several steps were taken to ensure it was used consistently. The provisional results of the analysis were reviewed and confirmed in a research team meeting. We also held group and individual feedback sessions with participants who corroborated our findings.

Finally, our research team included Māori, Pacific, and non-Māori non-Pacific researchers who were involved in the design, recruitment, interview, and analysis phases of the research, as well as in disseminating the results. In addition, we established an advisory group for the project to reflect and represent the interests and perspectives of people with type 2 diabetes, Māori, Pacific peoples, clinicians, and medicine safety specialists, and

we consulted this advisory group at the planning stage of the study regarding the proposed methods for recruiting and interviewing participants.

Our research also has some limitations. People who choose to take part in research are inevitably different from those who do not, so it is possible that there are other barriers to metformin adherence and persistence that were not identified in this study. For instance, despite our efforts to achieve a gender balance at the recruitment stage, about three quarters of those who agreed to take part were women. Future research could focus on exploring the views of men, especially those of Māori men, who were under-represented in this study.

Conclusions

In this qualitative study, participants identified several facilitators and barriers to taking metformin as prescribed. Having an understanding of patients' beliefs and experiences is key to improving medication adherence and persistence because, as the authors of a recent qualitative meta-synthesis concluded, while patients and healthcare providers share similar views about some of the barriers to adherence, there are also some differences.[43] In particular, the authors discussed the tendency of healthcare providers to attribute patients' sub-optimal adherence to a lack of motivation and insufficient understanding of the physiological and biomedical aspects of type 2 diabetes, whereas broader personal, social, and practical challenges are often foremost for people living with type 2 diabetes. Participants' feedback in our study has highlighted several actions (Table 6) that healthcare providers could take in the clinical setting to facilitate adherence.

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Table 6: Clinical implications of the findings.

- Recognise that the process of accepting the diagnosis of type 2 diabetes and the need for medication is a dynamic one that proceeds at different speeds for different patients, and progressively provide individually tailored information and support that is concordant with an individual's current stage of acceptance.
- Recognise and address feelings of personal failure and guilt that may have arisen from a lack of understanding about the progressive nature of type 2 diabetes.
- Reinforce beliefs about the positive aspects of taking metformin and address any misconceptions.
- Actively identify any reluctance to initiate metformin use and explore and address the reasons behind this reluctance.
- Proactively address potential side effects—for example, forewarn patients they may experience gastrointestinal upsets *and* what to do if they occur.
- Help patients to identify potential adherence-facilitating strategies that might work well for their particular circumstances.
- Recognise that most patients will miss a dose of metformin intermittently and pro-actively advise them what to do if that occurs.
- Involve partners and other family members, as appropriate, because they are often influential in facilitating medication adherence.
- Provide patients with visual evidence (eg, blood sugar and HbA1c graphs), especially early on, that metformin is improving glycaemic control.
- Ensure that patients are aware of, and have access to, various types of assistance for which they may be eligible (eg, prescription subsidies).
- Advise patients about trustworthy Internet sites for information about diabetes and its treatment.

Appendix

Appendix Table 1: Interview guide.

Topic areas and questions

Rapport-building initial questions regarding type 2 diabetes and metformin prescriptions
• To begin, would you mind sharing a little bit about yourself and your whānau (family)?
• Could you tell me about your diabetes?
  • When were you first diagnosed with diabetes?
  • How does diabetes affect your day-to-day life/work?
  • What does your whānau understand about your diabetes?
  • What sort of effect does your diabetes have on your whānau?
  • How do you manage your diabetes? *(e.g. medications, lifestyle)*
  • Who helps you to manage your diabetes?
• When were you first prescribed metformin?
• Is your doctor still prescribing metformin for you? ***If no**:* When did you stop taking metformin? What was the reason for stopping?

Questions related to Behavioural Beliefs *(i.e. perceived advantages and disadvantages of medication adherence)* • How did you feel about starting metformin? *If still taking*: How do you feel about taking it now? • What are the benefits of taking metformin? • How does/did taking metformin help you? • Can you tell me what you understand about how metformin works? • What are the things you don't/didn't like about taking metformin? • How does/did taking metformin affect your whānau and social life? Your work? *If relevant:* • How does metformin affect your mental/physical/spiritual/whānau wellbeing?
Questions related to Normative Beliefs: *(i.e. perceived social pressure regarding medication adherence or non-adherence)* • Who would approve of you taking metformin regularly? • Is their opinion important to you? Why? • Who would disapprove of you taking metformin regularly? • Is their opinion important to you? Why? *If relevant:* • How do you think your doctor/nurse/whānau feels about you not taking your metformin? How does this make you feel? • How important is it for you to follow your health professional's instructions about taking your metformin?
Questions related to Control Beliefs: *(i.e. perceived factors that impede or facilitate medication adherence)* • What are the things that help/helped you to take metformin regularly? • What situations make/made it easier for you to take metformin regularly? • Are there people who help/helped you to take metformin regularly? • What strategies have you/did you use to help you take metformin regularly? • What is/was the most challenging part of taking metformin regularly? • What situations make/made it difficult for you to take metformin regularly? • Are/were there people who make/made it difficult for you to take metformin regularly? *If relevant:* • Probe: household dynamics, family connectedness, social connectedness • What might be ways to fix any of the metformin-related problems you face/faced? • Where do/did you go, or who do/did you see, if you need/needed help with metformin issues?

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The emergence of azole resistance in Aspergillus fumigatus complex in New Zealand

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ABSTRACT

BACKGROUND: Azole resistance in *Aspergillus fumigatus (A. fumigatus)* is increasing globally. A pan-azole-resistant isolate prompted genetic analysis of local azole-resistant isolates to determine resistance genotypes.

METHODS: All *A. fumigatus* complex isolates were tested by the broth colorimetric micro-dilution method, Sensititre® YeastOne® (SYO) (TREK Diagnostic Systems, West Sussex, England). Epidemiological cutoff values derived from the Clinical & Laboratory Standards Institute method were used to determine the proportion of non-wild-type (non-WT) isolates (ie, those with an increased likelihood to harbour acquired mechanisms of resistance). Non-WT isolates were identified by ß-tubulin gene sequencing and the genotype for azole resistance was determined. The history of the patient with the first pan-resistant isolate was reviewed along with the treatment history of patients with azole-resistant strains.

RESULTS: From January 2001 to August 2020, antifungal susceptibility testing was performed on 260 *A. fumigatus* complex isolates: six isolates were non-WT for one or more azole agent, two *A. fumigatus sensu stricto* and four other members within the species complex: two *A. fischeri* and two *A. lentulus*. There were three non-WT isolates for amphotericin B, three for itraconazole, five for posaconazole and five for voriconazole. All six non-WT strains were isolated in the past nine years (P<0.01), and four in the past three years. Azole-resistance genotyping for the *A. fumigatus sensu stricto* isolates detected amino acid changes at hot spots in the *cyp51A* gene: one at G54E and one at G138C. All six isolates were WT for caspofungin. Five of the six patients with azole-resistant strains had previous azole treatment, and the patient with the pan-azole-resistant strain had been on continuous azole treatment for 42 months preceding strain isolation.

CONCLUSIONS: New Zealand can be added to the growing list of countries with azole-resistant *A. fumigatus* complex isolates, including pan-azole resistance in *A. fumigatus sensu stricto.* While uncommon and mostly found in cryptic species within the complex, azole resistance is increasing. The results provide a baseline for monitoring this emerging antifungal resistance trend in *A. fumigatus* in New Zealand.

Aspergillus spp. are the most common cause of invasive mould infections globally.[1,2] *Aspergillus fumigatus* (*A. fumigatus*) complex is the most frequently encountered group and molecular methods show it is comprised of more than 60 species, including *A. fumigatus* itself (*A. fumigatus sensu stricto*), *A. fischeri* and *A. lentulus.*[3,4] Species within the complex have varying susceptibility profiles.[4–8]

Triazoles are the cornerstone of recommended treatments for invasive aspergillosis (IA).[9] Azoles target an essential step in fungal ergosterol synthesis encoded by the *cyp51A* gene. Major mechanisms of azole resistance in *A. fumigatus* include mutations at hot spots in the *cyp51A* gene (target modification), alone or in combination with tandem repeats (TRs) in the gene's promotor region (over expression), or the upregulation of efflux pumps.[10,11] Hot-spot mutations are described in patients who have received courses of azole treatment, whereas TR-associated resistance has been linked to acquisition of environmental strains that have been exposed to azoles used in agriculture.[10, 12 –15]

Although there are no interpretive criteria for susceptibility or resistance for moulds, except with respect to voriconazole and *A. fumigatus sensu stricto*,[16] epidemiological cutoff values (ECVs) have been established for a limited number of species complex-antifungal agent pairings. An ECV defines the upper minimal inhibitory concentration (MIC) limit of wild-type (WT) isolates, without acquired resistance mechanisms, and non-wild-type (non-WT) isolates likely to harbour acquired resistance mechanisms.[17,18] ECVs do not group isolates into susceptible, likely to respond to treatment, resistant or unlikely to respond to treatment, but can be used when no interpretative criteria exist for identifying strains more likely to have acquired mechanisms of resistance and, by inference, less likely to respond to treatment.

We recently reviewed the antifungal susceptibility results of mould isolates performed in Auckland from 2001–2019.[19] Over the 19 years there were four *A. fumigatus* complex isolates that were non-WT for azole agents, but because molecular analysis of the *cyp51A* gene was not performed, their mechanisms of resistance was not known.[19] The 2020 isolation of a pan-azole-resistant *A. fumigatus sensu stricto* isolate prompted us to undertake genotype testing on local *A. fumigatus* complex isolates non-WT for azole agents to determine their mechanism of resistance.

Materials and methods

Isolates

All isolates tested were from Auckland City Hospital, or referred from other New Zealand laboratories, for the period January 2001–August 2020. The laboratory information system was interrogated to obtain a file of all *A. fumigatus* complex isolates that had anti-fungal susceptibility testing performed (detailed methods are reported elsewhere).[19] Isolates were initially identified by morphology.

Antifungal susceptibility testing

All isolates were tested by the broth colorimetric micro-dilution method, Sensititre® YeastOne® (SYO) (TREK Diagnostic Systems, West Sussex, England), following the manufacturer instructions. Endpoint interpretations followed Clinical & Laboratory Standards Institute (CLSI) methods.[16,20] The minimal inhibitory concentration (MIC) endpoint was defined as the lowest concentration producing complete inhibition of growth of amphotericin B (AMB), itraconazole (ITC), posaconazole (POS) and voriconazole (VCZ).[20] The minimal effective concentration (MEC) for the echinocandins (caspofungin, micafungin and anidulafungin) was defined as the lowest concentration producing small, rounded, compact hyphal forms compared to the hyphal growth of the growth control.[20] Readings were made at 24 hours for echinocandins and 48 hours for other agents. AMB and ITC were tested throughout the period. Other agents were tested as they were incorporated into the SYO assay, meaning not all agents were tested on each isolate.

To determine the proportion of non-WT isolates, CLSI ECVs for AMB (≤2mg/L), ITC (≤1mg/L) and VOR (≤2mg/L) were used.[18] CLSI has not published an ECV for POS, so the CLSI-based ECV published by Buil et al, ≤0.25mg/L, was used.[21] VOR susceptibility was defined as ≤0.5mg/L.[16]

Identification and resistance genotyping

All non-WT azole isolates were recovered from the culture collection water stocks and identified by β-tubulin gene sequencing.[3,22] Isolates were retested to confirm the MICs/MECs and their azole-resistance mechanism was determined by *cyp51A* gene sequencing.[23]

Case history and antifungal exposure

The notes of the patient with the first pan-azole resistant isolate of *A. fumigatus sensu stricto* were summarised and the electronic medical records of patients with the other non-WT azole isolates were reviewed to record azole exposure.

The two other New Zealand laboratories performing mould antifungal susceptibility testing were contacted and asked whether they had encountered any isolates with non-WT azole MICs.

Ethics

Cases were reviewed as part of the Australasian Society for Infectious Diseases Mycology Special Interest Group's Case Registry of *Aspergillus* infections. Health and

Disability Ethics Committee approval 20/NTB/35 and Auckland District Health Board institutional approval A+8799.

Results

Isolates

Over the 19.7-year period, 260 initial isolates of *A. fumigatus* complex isolates were tested and there were six non-WT isolates. Eighty one percent were from Auckland, with 65% from Auckland City Hospital. Table 1 shows the number of isolates tested for each antifungal, the identity of the six non-WT isolates (as determined by β-tubulin gene sequencing), their years of isolation, their susceptibility results and the proportion of non-WT strains..

During 2001–2010, no non-WT isolates were detected (143 tested). Six (5%) were detected 2011 to 2020 (117 tested), with a p-value of <0.01. Four of the six non-WT isolates were encountered in the past three years. All isolates were WT for caspofungin (MECs ≤0.5mg/L).[18]

The colonial appearance of both *Aspergillus fumigatus sensu stricto* isolates was typically blue-green with a suede-like surface, whereas the colony appearance of the other species varied from pale blue-green in *A. lentulus* to white floccose colonies in *A. fischeri*. The difference in colonial appearance on Sabouraud dextrose agar aided in recognising mixed cultures. Of the six isolates reported here (see Table 1), one *A. lentulus* (Isolate 4) and the two *A. fumigatus sensu stricto* were isolated in pure culture; one *A. lentulus* (Isolate 3) and one *A. fischeri* (Isolate 2) were isolated in mixed culture with a WT *A. fumigatus*; and one *A. fischeri* (Isolate 1) was isolated in mixed culture with a WT *A. fumigatus* and *Purpureocillium lilacinum*.

Genotypes

For the two *sensu stricto* isolates, different hot-spot mutations in the *cyp51A* gene were detected that resulted in amino acid changes at either Gly54Glu (G54E) or Gly138Cys (G138C) (Table 1). Neither isolate had TR mutations present. For *A. lentulus* and *A. fischeri* there was no amplification of the *cyp51A* gene, presumably due to mismatches in the primer binding regions.

Neither of the other laboratories performing susceptibility testing on *A. fumigatus* had encountered pan-azole resistant strains (J. Creighton and L. Sanders, personal communication). One had tested an isolate from a patient reported here (Isolate 5) and obtained the same results (J. Creighton, personal communication). The other laboratory had encountered a single isolate that was non-WT for POS, MIC=0.5mg/L (L. Sanders, personal communication).

Clinical history for pan-azole resistant isolate

Case 6 (Table 1) was a 61-year-old male who presented in December 2016 with six months of cough and breathlessness and an abnormal chest radiograph. He had been previously well, was a regular cyclist and a

Figure 1: (A) Calcified nodes (arrows). (B) Intracavity body (arrow).

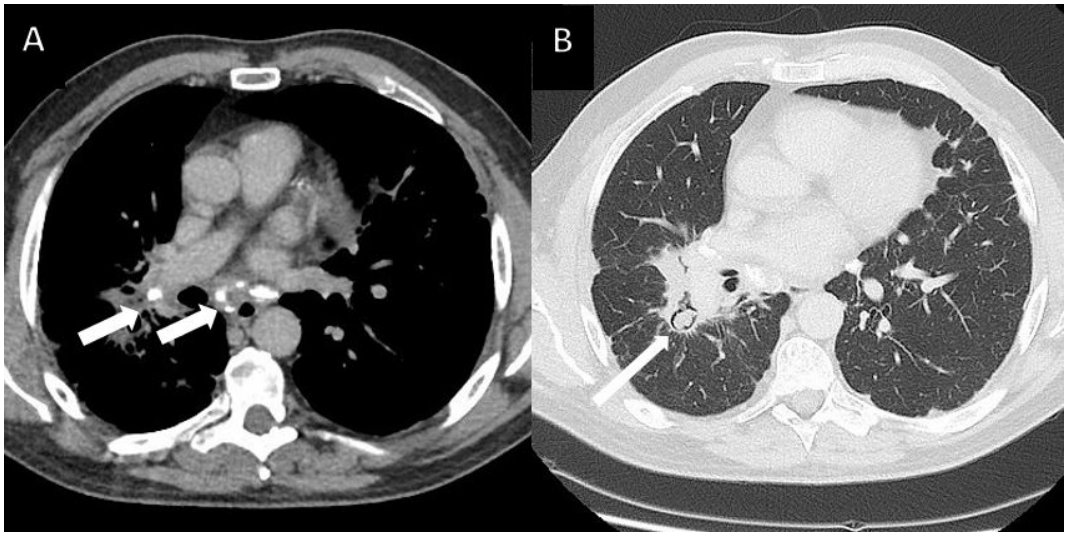


Table 1: Antifungal susceptibility results (mg/L) for amphotericin B and azoles against *Aspergillus fumigatus* complex isolates: January 2001–August 2020.

Antifungal agent			**Amphotericin B**	**Itraconazole**	**Posaconazole**	**Voriconazole**	
Interpretive criteria for wild-type (WT) isolates (mg/L)[1]			≤2	≤1	≤0.25	≤1	
Isolates tested			260	260	215	238	
Non-WT isolates[2] (year isolated)	Specimen type	Clinical background					Resistance genotype
1. *A. fischeri*[3] (2018)	B. wash[4]	Lung transplant	1	0.5	0.25	2	Not determined
2. *A. fischeri*[3] (2020)	B. wash	Lung transplant	2	0.5	0.5	2	Not determined
3. *A. lentulus* (2015)	B. wash	ALL and BMT[5]	8	1	0.5	4	Not determined
4. *A. lentulus* (2011)	B. wash	AML and BMT[5]	8	2	1	8	Not determined
5. *A. fumigatus sensu stricto* (2018)	Sputum	Cystic fibrosis	2	>16	2	0.25	Gly54Glu(G54E)[7]
6. *A. fumigatus sensu stricto* (2020)	Lung cavity	Sarcoidosis	4	>16	2	>8[6]	Gly138Cys(G138C)[7]
Total non-WT (%)			3 (1.2%)	3 (1.2%)	5 (2.3%)	5 (2.1%)	

[1] Clinical Laboratory Standards Institute (CLSI) criteria used for amphotericin B, itraconazole and voriconazole.[18] Posaconazole criterion from CLSI based methods.[21]
[2] All non-WT isolates identified by β-tubulin gene sequencing.
[3] Synonyms: *Aspergillus thermomutatus* (anamorph) and *Neosartorya pseudofischeri* (teleomorph).
[4] Bronchial washing/alveolar lavage specimen.
[5] ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; BMT, bone marrow transplant.
[6] For *A. fumigatus sensu stricto* the interpretive criteria for voriconazole susceptibility is ≤0.5 mg/L.[16]
[7] No *cyp51A* gene tandem repeat mutations detected.

lifelong non-smoker. Medications included anti-inflammatory agents and amitriptyline for back pain; he had required a laminectomy 25 years before.

CT chest showed multiple calcified mediastinal nodes (Figure 1A) and bilateral cavities with one containing an intracavitary body, a presumed fungal ball (aspergilloma), (Figure 1B).

Endo-bronchial ultrasound guided fine needle aspiration of a mediastinal node revealed non-necrotising granulomas. Bronchial washings grew an *Aspergillus fumigatus* complex isolate, which was identified by morphology, with negative molecular and culture tests for *Mycobacterium tuberculous* (TB). Susceptibility testing was not performed on this isolate. QuantiFERON-TB Gold and anti-neutrophil cytoplasmic antibodies were negative. The angiotensin converting enzyme level was normal. *Aspergillus* serology was positive with *Aspergillus* RAST of 3+ and *Aspergillus* specific IgG elevated at 48mg/L (expected <40mg/L). The static and dynamic lung functions were within normal limits.

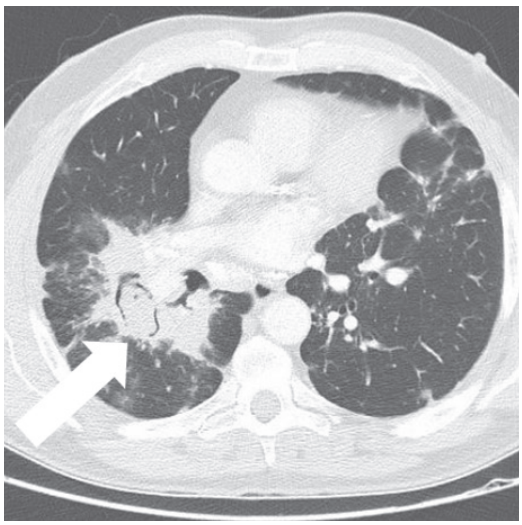
He was diagnosed with chronic cavitary pulmonary aspergillosis on background sarcoidosis and in early 2017 was commenced on itraconazole 200mg twice daily. This was changed to voriconazole 200mg twice daily in April 2018 when six month's funding became available. When funding expired, he reverted to itraconazole in October 2018 for two months before recommencing voriconazole in December 2018. This was self-funded from an overseas supplier from December 2018, although he did occasionally take itraconazole depending on his supply of voriconazole and to reduce cost.

In March 2017 a cardiology opinion was sought in view of the symptoms of breathlessness in the presence of normal lung-function tests. A coronary angiogram confirmed obstructive coronary disease requiring a complex multi-vessel coronary revascularisation followed by dual antiplatelet therapy with aspirin and clopidogrel. A cardiac MRI showed a mildly dilated left ventricle with ejection fraction of 45% and no evidence of cardiac sarcoidosis.

In April 2018, while on dual antiplatelet therapy and itraconazole, he developed moderate volume haemoptysis. There was no accessible vessel amenable for bronchial artery embolisation. The haemoptysis resolved with cessation of clopidegrol and the commencement of voriconazole.

During the subsequent 16 months he continued to have episodes of mild, intermittent haemoptysis, which led to a large volume haemoptysis in August 2020. The voriconazole level obtained at this time was therapeutic at 2.6mg/L (goal 1–5 mg/L). A CT chest showed enlarging bilateral lung cavities and a presumed aspergilloma in the right lung (Figure 2).

Figure 2: Chest CT after 42 months of continuous azole treatment. Lung cavities had enlarged and a larger intracavitary body is present in right lung (arrow).



A bronchial artery embolisation was attempted but was unsuccessful, so he underwent a right pneumonectomy. The resected lung showed a large lung cavity with a fungal ball. Histopathology revealed the features of sarcoidosis with multiple non-necrotising granulomas in both the lung and mediastinal nodes. The necrotic material in the centre of the cavity was an aspergilloma consisting of a dense mass of septate acute-angled branching hyphae.

Samples of the viscous cavity contents were obtained for mycology. Direct examination showed large amounts of dichotomously branching hyphae, and culture recovered *Aspergillus fumigatus sensu stricto*. Antifungal susceptibility results and azole resistance genotype are shown in Table 1 (Case 6).

Azole exposure before isolation of non-WT isolates

Case 1 had no previous azole treatment. Case 2 had three previous six-month courses of either voriconazole, in 2015 and 2016, or posaconazole, in 2017. The isolate was obtained two and a half years after last azole treatment. Case 3 had four months of fluconazole prophylaxis following bone-marrow transplant and was on fluconazole at the time of isolation. Case 4 had past posaconazole prophylaxis when undergoing remission induction chemotherapy for acute myeloid leukaemia and voriconazole for fungal lung infection eight months earlier. They were also treated with amphotericin B and were off azole treatment at the time of isolation. Case 5 had itraconazole treatment of unknown duration(s) for allergic bronchopulmonary aspergillosis, which was stopped in early 2014. Itraconazole was recommenced for four and a half months, stopping mid-April 2018. The sputum isolate was obtained late May 2018 when the patient was off azole treatment.

Discussion

A. fumigatus complex contains subspecies (eg, *A.fumigatus sensu stricto* and many other 'cryptic' species) that are difficult to distinguish by conventional testing methods and require molecular methods for correct identification.[3,4] This study establishes the low rate of azole resistance in *A. fumigatus* complex in New Zealand and the current rarity of pan-azole-resistant *A. fumigatus sensu stricto*. All non-WT isolates were encountered in the past 10 years, and most in the last three. Most non-WT isolates were cryptic species within the complex. Three of the non-WT isolates were in mixed culture with WT *A. fumigatus* isolates. Mixed cultures have been reported before and underscore the need to carefully inspect cultures to detect colonial variants.[14] The AMB MIC for both *A. lentulus* isolates (8mg/L) appears higher than that reported for five Australian isolates (all ≤2mg/L). However, the small numbers, as well as biological and inter-laboratory variability, limit comparison between our countries.[3,19] Others have reported the high MICs we observed for amphotericin in *A. lentulus* isolates.[6,24]

Azole resistance in *A. fumigatus* was first found in isolates obtained in the late 1980s. Resistance is now encountered in many countries (3.2% prevalence, range 0–26%).[25] Resistance may vary within a country[12] and can increase significantly within five years.[26] In Spain 7.4% of 847 *A. fumigatus* clinical isolates from 2019 were azole resistant, with a significant subspecies difference (5.5% *A. fumigatus sensu stricto*, n=828, vs 95% in cryptic species, n=19).[27] Importantly, cross-resistance within the class is common, which limits treatment options.[26,28] Resistant isolates are encountered in azole-naive patients and the mortality rate for azole-resistant invasive aspergillosis is often very high.[12,14]

Azole resistance is uncommon in Australia (approximately 2%).[29,30] It is reassuring that the non-WT for azole agents was low in New Zealand (1.2–2.1% of isolates tested), and complete azole cross-resistance was only observed in one *A. lentulus* and one *A. fumigatus sensu stricto*, which was also categorised as VOR resistant by the recently published CLSI interpretive criterion.[16]

We did not attempt TR genotyping on the non-*sensu stricto* isolates, because the primers for *A. fumigatus sensu stricto* do not amplify the region in cryptic species in the complex. The proportion resistance due to TR and hot-spot mutations varies significantly between countries. In the Netherlands, for isolates known to have *cyp51A* mutations, 90% and 10% were due to TR and hot-spot mutations, respectively, with 35% having neither type of mutation detected.[31] In a UK series, however, where most isolates were from patients with chronic pulmonary aspergillosis (CPA) and previous azole treatment, hot-spot mutations dominated (>90%) and TR mutations were uncommon (<5%).[26] In Australia the proportion of hot-spot, TR or no-*cyp51A* mutations detected in 12 isolates were 50%, 25% and 25%, respectively.[29,30] Although we did not detect TR mutations in *A. fumigatus sensu stricto*, their future occurrence in New Zealand is possible because, even though they comprise only a small proportion of all fungicide use, triazole fungicides are used in agriculture in New Zealand.[32] However, information on the use of triazole in agriculture is more than 15 years old, and we know of no contemporary data on the extent

of environmental use of triazoles on our crops. We support the call for better surveillance on pesticide use in New Zealand.[32] The isolation of a non-WT azole isolate in an azole-naive patient should arouse suspicion of TR mutations, and resistance genotyping should be performed.

Currently there is a limited understanding of the resistance mechanisms operating in the cryptic species within the complex, some of which are described as having intrinsic azole resistance.[4,5,6,11,24] The *cyp51A* gene and its promotor region that detect either hot-spot or TR mutations are different for *A. fumigatus sensu stricto* and cryptic species such as *A. lentulus* and *A. fischeri*.[7,33] The non-amplification of *cyp51A* we encountered reflects this. More sequence data are required to understand the resistance mechanisms in these species.

Triazoles are not known to be mutagenic and therefore resistance is selected when genetic variation occurs in the progeny of *Aspergillus* species.[34] The most recognised resistance mechanisms occur either in triazole-treated patients, hot-spot mutations (found in Case 5 and Case 6) or in isolates from environments that have been exposed to triazole fungicides, TR mutations. The former is more likely to occur in patients with CPA on azole treatment due to pulmonary cavities where *A. fumigatus* can undergo asexual sporulation, which is more prone to mutations.[34] The clinical impact of azole resistance has been unclear, as many earlier studies with small patient numbers have not shown outcome differences. In a recent report of a large multicentre retrospective cohort, mortality at both 42 days and 90 days was statistically higher (21% and 25%, respectively) in aspergillosis due to triazole-resistant versus triazole-susceptible strains.[35]

The interplay of the human immune system and *Aspergillus* largely determines the pattern of clinical illness, which can range from IA seen predominantly in haematopoietic, solid-organ transplant and neutropenic patients, to allergic bronchopulmonary aspergillosis seen predominantly in immunocompetent people with a hyperimmune response.[2] CPA represents a mid-spectrum seen mostly in patients with underlying lung disease and who are not overtly immunocompromised. CPA can occur in those with previously treated TB, non-tuberculous mycobacteria or bronchiectasis. Aspergillosis was reported in 2% of a cohort of sarcoidosis patients.[36] CPA usually affects middle-aged men and presents in an indolent fashion with constitutional symptoms (malaise, anorexia, sweats), chronic cough with occasional haemoptysis and shortness of breath. Slow and evolving lung cavities, usually with thick walls and either with or without a fungus ball (aspergilloma), are typical of CPA and were observed in Case 6.[2] Treatment of CPA is challenging due to a high relapse/recurrence rate of up to 25% despite prolonged treatment (>12 weeks). The anti-fungal treatment for CPA is suppressive rather than curative and those with progressive disease require lifelong antifungal therapy.[2] CPA is associated with high mortality, with 27% over a mean follow-up duration of 30 months and 50% over five years in separate studies.[37,38] In the face of worsening symptoms, or progressive disease, strong consideration should be given to obtaining deep respiratory samples to the determine antifungal susceptibility of the patient's isolate(s) to enable treatment optimisation. In addition, therapeutic drug monitoring is recommended for voriconazole because genetic polymorphisms in cytochrome P450 are responsible for significant inter-patient pharmacokinetic variability resulting in phenotypes ranging from poor to super metabolisers, both of which may require dose adjustments to prevent toxicity or improve efficacy, respectively.[39]

While both European and US guidelines recommend susceptibility testing for epidemiological purposes, they differ in recommendations for routine testing. The European guideline recommends susceptibility testing unless the patient is azole-naive and from a region without resistance found in surveillance programmes.[40] Given the low rate of resistance, the US guideline does not recommend routine testing unless the isolate has atypical growth or there are clinical concerns for resistance.[41] We consider it prudent to perform susceptibility testing for clinically significant isolates from a lower respiratory tract specimen, or from an immunocompromised host with invasive infection or an immunocompetent host with cavitatory lung infection. If a prolonged (>12

week) treatment course is planned, initial susceptibility testing should be performed, as it would be before initiating long-term anti-bacterial or anti-mycobacterial treatment.

Currently, funding for voriconazole is available only for six months for immunocompromised patients with proven, probable or possible invasive aspergillosis. The better bioavailability of voriconazole and probably higher mortality with resistant strains has shifted treatment choice in favour of voriconazole, especially in those with extensive CPA.[2] We suggest the indications for voriconazole should be extended to include patients with CPA requiring long-term treatment.

Our study has strengths and limitations. Most isolates came from Auckland, a city with the country's largest population and concentration of tertiary/quaternary clinical services. The testing was performed by a small number of staff using the same method in one laboratory. All isolates had their MICs/MECs confirmed by repeat testing and the susceptibility profiles were consistent with other reports[4,6,24] Molecular methods determined the identification of all the non-WT isolates. However, this report has limitations. Although our data are not a complete summary of testing in the country, as two other laboratories also perform mould susceptibility testing, neither of these laboratories have encountered pan-azole resistance. The isolates were deemed relevant enough to have susceptibility testing performed, but we do not know the proportions reflecting proven or likely infection or colonisation. In addition, isolates are not always obtained from patients treated for suspected aspergillosis, meaning the denominator data underestimate the burden of *Aspergillus* infection in New Zealand. CLSI methods do not always result in high MICs for all azoles in isolates with known resistance mechanisms and may not detect reduced susceptibility for all mutations (ie, our testing may have missed some isolates with *cyp51A* mutations).[31]

In conclusion, New Zealand can be added to the growing list of countries with azole-resistant *A. fumigatus* complex isolates, including pan-azole resistance in *A. fumigatus sensu stricto.* Although uncommon and mostly found in cryptic species within the complex, azole resistance is increasing. Our results provide a baseline for monitoring this emerging antifungal resistance trend in *A. fumigatus* in New Zealand.

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Nil.
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Primary medication non-adherence to analgesics and antibiotics at Counties Manukau Health Emergency Department

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ABSTRACT

AIM: To measure primary medication non-adherence to antibiotics, paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in patients discharged from Counties Manukau Health Emergency Department (CMH-ED).

METHOD: A retrospective observational study based on 1,600 discharged patients' data collected between 28 April–6 May and 28 July–9 August 2014. Data were included for patients who were residents within the Auckland Regional Public Health Service boundaries, presented to CMH-ED and were discharged with a prescription.

RESULTS: Of 992 patients, 48.5% did not have at least one medication on their discharge prescription filled. Patients were mostly born in New Zealand (66.5%), of Pacific Island descent (42.8%), living in the most socioeconomically deprived areas (78.1%) and under 10 years of age (32.6%). Filling rates significantly increased with >1 prescribed item ($p \leq 0.01$). NSAIDs were significantly more likely to be filled compared with paracetamol (59.9% vs 51.3%, $p=0.034$); antibiotics were significantly more likely to be filled than all other medicines (80.4%, $p<0.001$). The most significant predictors for non-adherence when accounting for number and types of medications were patients 10–44 years ($p<0.05$) and smokers ($p<0.01$).

CONCLUSIONS: Age, smoking and number of prescribed medications were predictors of non-adherence to medication type. Further research is warranted to assess whether changes to prescription co-payments affect the rate of nonadherence.

For medication to be therapeutically effective, it is essential that patients adhere to them. Filling a prescription is the first critical step to establish medication adherence.[1,2] Research on medication adherence has primarily focused on secondary non-adherence, which occurs when patients don't take their medicines as prescribed, don't refill their prescriptions on time or stop taking their medicines.[3] However, rates of primary medication non-adherence, where a patient fails to have a prescription filled for newly prescribed medicines or a suitable alternative within a specified timeframe, are far less known.[3,4] Failing to get newly prescribed medications filled places a burden on patients, families and the broader healthcare system by increasing mortality/morbidity, hospitalisation rates and/or emergency department (ED) visits, and it is associated with greater economic cost.[5–7] Previous studies have estimated that around 7–35% of patients in EDs fail to fill new prescriptions,[6,8] and in paediatric EDs the reported percentage is as high as 66%.[9]

Non-adherence occurs due to a dysfunctional triad of patient, healthcare-system and contextual influences,[5–7,10] including a lack of financial and social support, the availability and/or accessibility of healthcare resources, the severity of disease and the available treatment options.[11] In the ED, primary medicine non-adherence is comparatively higher in patients with financial

constraints.[12–16] Patients under financial constraints may select to have certain medicines filled over others, or may be unwilling to pay for a medicine to use in the short term.[6,17] In some cases, patients may also be unaware of the importance of the prescribed medicine, or may have a supply at home.[6,17]

Previous research found that 16% of patients discharged on 'high importance' medication exhibited primary non-adherence 30 days after discharge.[7] These prescriptions included medications such as antibiotics for the treatment of acute infections such as pneumonia, urinary tract infections and cellulitis.[7] Non-adherence to antimicrobial agents carries additional healthcare costs due to treatment failure, readmission to ED and resources being wasted on unused medication.[7,18] In the ED, adherence to antibiotics has been reported as low as 30–40%.[18] Analgesics are often considered to be of lesser importance compared with antibiotics, but pain is one of the most common reasons why patients visit an ED.[19] Although non-adherence to pain relief is generally not life-threatening, failure to receive adequate analgesia can result in significant morbidity.[7] Studies suggest that a significant proportion of ED prescriptions for analgesics remain unfilled[8,19] due to patients reporting a lack of pain, having a home supply, a fear of medication side effects or believing the analgesic is not strong enough.[19]

Non-adherence is also found to increase if patients are prescribed two or more medicines,[6,16] lack access to primary care physician,[20] cannot access a community pharmacy at time of discharge[19] or are tobacco smokers.[11] Patient demographic factors such as age, gender and ethnicity are also thought to influence medication adherence[21–23] but are inconsistently reported in the literature.[12,16]

In New Zealand, little is known about primary medication non-adherence in the ED. Previously we explored the relationship between non-adherence to primary medication and patient sociodemographics, smoking status, access to a regular GP and discharge time and/or day.[24] The aim of this study was to measure primary medication non-adherence to antibiotics, paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in discharge prescriptions from Counties Manukau Health Emergency Department (CMH-ED), and to determine which patient factors are likely to influence patients' decisions to fill prescriptions for these three medication classes.

Method

This was a retrospective, observational study design of patients discharged from CMH-ED. Ethics approval was granted by the University of Auckland Human Participants Ethics Committee (Reference No. 012463) and Counties Manukau District Health Board Ethics Committee.

Participant selection

Data were collected in September from the first 1,000 patients discharged from CMH-ED between 28 April–6 May 2014, and further data were collected in January 2015 from 600 additional patients between 28 July–9 August 2014. The data were purposefully collected on these weeks to facilitate comparison between autumn and winter seasons, and the dates allowed for an assessment of adherence >90 days after the prescription order.

Data were included for patients who were residents within the Auckland Regional Public Health Service boundaries, presented to CMH-ED and were discharged with a prescription for one or more medicines. Patients were excluded if they were admitted to another ward, were transferred to another hospital, left CMH-ED without seeing a doctor or were discharged without a prescription.

Data collection

Patient data were identified through CONCERTO™ (a software programme that coordinates patient data across the whole Auckland region in a central electronic platform) by limiting the search to 'ED speciality' and selecting the dates required. To maintain patient confidentiality, and for auditing purposes, each patient was allocated a unique identifying code linked to their National Health Index (NHI) number. If any patients presented to the ED more than once during the study period, only their first discharge was analysed.

To facilitate data collection, a paper-based tool was developed and piloted for efficiency. Age, gender, country of birth, residential suburb, ethnicity, language spoken and details of each patient's regular

primary physician were collected if available. Presenting indication, discharge date and time, smoking status and medicines provided on discharge were obtained from electronic and paper discharge summaries. To determine whether patients had their ED prescriptions filled, information from community pharmacies was retrieved via TestSafe™, accessed via CONCERTO™. TestSafe™ records the medicines prescribed to patients via their NHI, how many medicines were filled at each dispensing, the date of dispensing and the contact details of the dispensing community pharmacy.

Data entry

Data were entered into Microsoft Excel™, and variables were coded for further analysis. Population data from Stats NZ were used to group ethnicity data into various categories. Ministry of Health guidelines assisted age categorisation, with patients under 25 years further divided into categories: under 10 years, 10–17 years (adolescent) and 18–24 years (young adults). Suburb deprivation was coded using the New Zealand Index of Deprivation (NZDep2013).[25] All other categories were grouped according to the information available in the patient notes. Occupation included patients under the age of five years, who were classed as 'infants/children', and those of school-going age (5–17 years) and/or undergoing tertiary/other education were grouped as 'students'. Although 'others' were adults of employable age (18–65 years), their employment status was unclear and hence were grouped as a separate class.

Data validation

Of the total patient dataset, 20% were randomly selected using the Microsoft Excel™ randomisation function (=RANDBETWEEN) and manually cross-checked by two researchers to confirm data-entry reliability. A further 50 patients were selected by the same randomisation method and telephoned using a pre-scripted telephone checklist to enquire whether they had collected their medicine from a pharmacy following discharge. This was compared to available TestSafe™ data to ensure triangulation of the data.

Analysis

Adherence to the three medication classes of interest was analysed by the proportion of prescribed medicines that were filled. Poisson regressions were conducted with a generalised linear model with the log of the total filled per medication class per person as the offset to evaluate medication adherence. Poisson regression with one explanatory variable is given, as well as multivariable regression. Bivariable regression was added to evaluate univariable effect on adherence per medication type. All possible two-way and some relevant three-way interaction terms were evaluated to find the model of best fit. The model with the minimum Akaike Information Criterium (AIC) value was used as the best-fit multivariable model.[26] The evaluated independent (categorical) variables were age, ethnicity, gender, country of birth, suburb deprivation, language, occupation, regular GP, smoking, discharge date, discharge day and discharge time, medication type and total number of medications prescribed. There were no missing data in the response variables (number of filled medicines and total number prescribed per medicine). An extra level, 'unknown', was constructed for the missing values in the explanatory categorical variables. Priory pairwise comparisons were made to group the levels within the categorical variates, using the covariance matrix as derived from the final multivariable model. All parameters denoted by the same letter (ie, a, b, c or d) within a group are not significant from each other, and alpha is 0.05. All analyses were conducted using R (version 4.01, 64 bit).

Results

Of 1,600 patients, data were excluded for 608 because they either were discharged without a prescription (n=470; 29.4%), left without seeing a doctor (n=70; 4.4%), were non-Auckland residents (32; 2%), were admitted to a ward (n=19; 1.2%) or were transferred to another healthcare facility (n=12; 0.8%), or incomplete data were provided for them (n=5; 0.3%).

Patients were predominantly born in New Zealand (n=660; 66.5%), of Pacific Island descent (n=425; 42.8%), 24 years or younger (n=559; 56.4%) and living in the most socioeconomically deprived suburbs (NZDep2013 9 & 10) of Auckland (n=775; 78.1%). The majority were non-smokers (n=804; 81.1%) and had a regular GP (n=958; 96.6%). Almost

a quarter (n=238; 23.4%) presented to the CMH-ED on a Monday, and close to half (n=481; 48.5%) were discharged between 8pm and 8am.

The majority (n=893; 90%) were discharged with a prescription for three medicines or less: of these, 29.2% (n=290) were prescribed one medication, 36.5% (n=362) were prescribed two medications and 24.3% (n=241) were prescribed three medications. The remaining 10% (n=99) were prescribed four or more medicines. Patient data were categorised by the type of medication prescribed (Table 1).

Almost half (n=480; 48.4%) of the patient sample did not have at least one medication item on their prescription filled. Univariable analysis found filling rates significantly increased when patients were prescribed more than one medication ($p \leq 0.01$) (Table 2). Compared with paracetamol (51.3%), NSAIDs (59.9%) and other medications (61%) were significantly more likely to be filled ($p=0.034$ and $p=0.023$, respectively). Antibiotics were significantly more likely to be filled than all other medication ($p<0.001$). Bivariable analyses with medication type showed the strongest associations with age, smoking and number of prescribed items (Appendix Tables 1–4). Compared to patients under 10 years, patients 10–17 years were significantly less likely to have NSAIDs filled ($p=0.036$) and patients 10–24 years were significantly less likely to have paracetamol prescriptions filled ($p \leq 0.023$). Smokers were significantly less adherent to paracetamol ($p=0.022$) and other medication ($p=0.034$). Paracetamol was significantly more likely to be filled if other items were also prescribed, as were other medications if three or four items were co-prescribed ($p \leq 0.01$). Patients born outside of New Zealand were more likely to fill NSAIDs ($p=0.027$). No significant differences were found for antibiotics. Univariable analysis has been described more fully elsewhere.[24]

The best multivariable model for adherence included age, smoking and the two-way interaction medication type and number of medications prescribed (Table 3). This data confirmed that, compared with paracetamol alone, patients who were prescribed more than one item were significantly more likely to have their prescriptions filled ($p<0.01$) (Figure 1). Antibiotics, NSAIDs (if not the only item prescribed) and other medications were all significantly more likely to be filled compared with paracetamol ($p<0.01$).

Discussion

In this study, 90% of patients were prescribed between one and three medications on discharge from CMH-ED, and almost half did not have at least one medication filled within 90 days. Patients were more likely to have their prescription filled when more than one medication was prescribed. Antibiotics, NSAIDs and other medications were significantly more likely to be filled compared with paracetamol alone ($p<0.01$). When accounting for number of medication items and type of medication, the most significant predictors for non-adherence were patients aged 10–44 years and smokers ($p<0.01$).

Literature has shown variable effects from age and income on whether prescriptions are filled. Some studies have revealed that older children were less likely to have their prescriptions filled,[9] as are those who were of low income or vulnerably housed,[9,20] whereas other studies have found no associations.[6,9] In our study, the lowest rates of prescription filling for all medication types were in children aged 10–17 years, which was significant compared to children under 10 years ($p<0.001$). It is important to note that, at the time of this study, the prescription co-payment charge was NZ$5 per item, a $2 increase from the previous year (2013). This co-payment was applied to all patients over the age of six years, regardless of income status,[27] and may have contributed to children under the age of 10 having higher prescription filling rates than older children. The co-payment increase was found to result in some patients delaying or avoiding filling their prescription and/or selecting to fill only certain medicines they deemed more important.[27] It has also been proposed that poorer adherence in younger patients may be due to less established or noncontinuous relationships with a primary care physician,[11] since in an ED setting prescribing clinicians are typically unfamiliar with the patient's lifestyle and/or resources.[28] In this study, prescription filling rates of all medication types were much lower in those who did not have a regular

Table 1: The total number of medications prescribed and the percentage of medication types filled, as characterised across different patient variables (N=992).

	Paracetamol n/n filled (%)		NSAIDs n/n filled (%)		Antibiotics n/n filled (%)		Other n/n filled (%)		Total n/n filled (%)	
	684	(51.3)	676	(59.9)	260	(80.4)	569	(61.0)	2189	(59.9)
Gender										
Male (n=495; 49.9%)	359	(52.6)	370	(63.0)	124	(80.6)	251	(63.7)	1104	(61.8)
Female (n=497; 50.1%)	325	(49.8)	306	(56.2)	136	(80.1)	318	(58.8)	1085	(58.1)
Age										
< 10 (323; 32.6%)	233	(57.9)	120	(67.5)	97	(84.5)	129	(68.2)	579	(66.7)
10–17 (116; 11.7%)	89	(33.7)	87	(44.8)	22	(63.6)	44	(50.0)	242	(43.4)
18–24 (120; 12.1%)	82	(36.6)	114	(50.0)	31	(77.4)	69	(58.0)	296	(51.0)
25–44 (215; 21.7%)	151	(51.0)	196	(58.7)	51	(82.4)	145	(57.2)	543	(58.4)
45–64 (159; 16%)	107	(58.9)	139	(71.2)	44	(75.0)	128	(63.3)	418	(66.0)
> 64 (59; 5.9%)	22	(72.7)	20	(70.0)	15	(93.3)	54	(61.1)	111	(69.4)
Ethnicity										
MELAA[a] (17; 1.7%)	12	(91.7)	13	(92.3)	3	(100)	8	(50.0)	36	(83.3)
NZ European (213; 21.5%)	138	(53.6)	156	(64.1)	52	(92.3)	119	(63.9)	465	(64.1)
Asian (157; 15.8%)	111	(55.0)	123	(60.2)	34	(73.5)	86	(65.1)	354	(61.0)
Pacific (425; 42.8%)	290	(51.7)	252	(61.1)	122	(80.3)	246	(59.8)	910	(60.3)
Māori (175; 17.6%)	128	(41.4)	127	(48.8)	49	(71.4)	107	(57.0)	411	(51.3)
Unknown (5; 0.5%)	5	(40.0)	5	(60.0)	0	(0.0)	3	(100)	13	(61.5)
Country of birth										
Outside NZ (282; 28.4%)	189	(57.7)	225	(68.9)	75	(82.7)	197	(59.9)	686	(64.7)
NZ (660; 66.5%)	461	(48.4)	413	(54.7)	177	(79.1)	332	(63.0)	1383	(57.7)
Unknown (50; 5%)	34	(55.9)	38	(63.2)	8	(87.5)	40	(50.0)	120	(58.3)
Suburb NZDep2013 index[b]										
1 (9; 0.9%)	7	(57.1)	11	(72.7)	0	(0.0)	3	(66.7)	21	(66.7)
2 (23; 2.3%)	13	(46.2)	22	(50.0)	3	(33.3)	9	(44.4)	47	(46.8)
3 (16; 1.6%)	10	(50.0)	13	(76.9)	5	(100)	4	(50.0)	32	(68.7)
4 (44; 4.4%)	35	(65.7)	39	(64.1)	9	(88.9)	20	(65.0)	103	(67.0)
5 (18; 1.8%)	12	(66.7)	13	(69.2)	6	(83.3)	9	1(00.0)	40	(77.5)
6 (43; 4.3%)	25	(60.0)	29	(62.1)	15	(73.3)	32	(75.0)	101	(67.3)
7 (35; 3.5%)	29	(55.2)	29	(69.0)	6	(100)	12	(75.0)	76	(67.1)
8 (25; 2.5%)	18	(55.6)	16	(62.5)	6	(83.3)	11	(45.5)	51	(58.8)
9 (370; 37.3%)	259	(45.2)	235	(54.5)	104	(75.0)	211	(64.0)	809	(56.6)
10 (405; 40.8%)	273	(53.5)	267	(61.8)	105	(84.8)	253	(56.1)	898	(60.4)
Unknown (4; 0.4%)	3	(33.3)	2	(50.0)	1	(100)	5	(40.0)	11	(45.5)

Table 1: The total number of medications prescribed and the percentage of medication types filled, as characterised across different patient variables (N=992) (continued).

	Paracetamol n/n filled (%)		NSAIDs n/n filled (%)		Antibiotics n/n filled (%)		Other n/n filled (%)		Total n/n filled (%)	
	684	(51.3)	676	(59.9)	260	(80.4)	569	(61.0)	2189	(59.9)
Language										
Non-English (61; 6.2%)	40	(55.8)	31	(61.3)	13	(76.9)	30	(73.3)	117	(64.1)
English (877; 88.4%)	604	(51.2)	612	(60.0)	230	(80.9)	520	(60.2)	1966	(59.8)
Unknown (54; 5.4%)	37	(48.6)	33	(57.6)	17	(76.5)	19	(63.2)	106	(58.5)
Occupation										
Other (171; 17.2%)	125	(59.2)	173	(67.1)	43	(88.4)	109	(69.7)	450	(67.6)
Infant/child (236;23.8%)	175	(58.3)	90	(66.7)	62	(83.9)	85	(70.6)	412	(66.5)
Retired (51; 5.1%)	20	(65.0)	16	(62.5)	14	(92.9)	47	(59.6)	97	(66.0)
Employed (143; 14.4%)	100	(49.0)	126	(62.7)	37	(78.4)	99	(56.6)	362	(58.8)
Student (228; 23%)	162	(45.1)	144	(55.6)	61	(80.3)	113	(57.5)	480	(55.6)
Unemployed (77; 7.8%)	47	(36.2)	64	(46.9)	19	(73.7)	60	(46.7)	190	(46.8)
Homemaker (66; 6.7%)	41	(36.6)	45	(40.0)	19	(57.9)	46	(54.3)	151	(45.7)
Unknown (20; 2.0%)	14	(57.1)	18	(66.7)	5	(60.0)	10	(90.0)	47	(68.1)
Regular GP										
Yes (958; 96.6)	662	(51.4)	654	(60.4)	249	(81.5)	552	(61.2)	2117	(60.3)
No (34; 3.4%)	22	(50.0)	22	(45.5)	11	(54.5)	17	(52.9)	72	(50.0)
Smoking										
No (804; 81.1%)	557	(54.0)	511	(61.6)	200	(82.0)	437	(64.3)	1705	(62.2)
Yes (139; 14.0%)	93	(35.5)	123	(55.3)	48	(75.0)	102	(46.1)	366	(50.3)
Unknown (49; 4.9%)	34	(50.0)	42	(52.4)	12	(75.0)	30	(63.3)	118	(56.8)
Total number of medications prescribed										
1 (290; 29.2%)	121	(24.8)	35	(42.9)	56	(78.6)	78	(42.3)	290	(42.1)
2 (362; 36.5%)	278	(52.2)	248	(51.2)	58	(84.5)	140	(57.1)	724	(55.4)
3 (241; 24.3%)	197	(60.9)	261	(65.1)	96	(80.2)	169	(68.6)	723	(66.8)
4 (71; 7.2%)	63	(66.7)	100	(71.0)	37	(70.3)	84	(79.8)	284	(72.5)
>4 (28; 2.8%)	25	(56.0)	32	(68.8)	13	(100)	98	(52.0)	168	(59.5)
Discharge month										
Autumn (n=511;51.5%)	339	(54.3)	346	(61.0)	134	(85.8)	343	(60.6)	1162	(61.8)
Winter (n=481;48.5%)	345	(48.4)	330	(58.8)	126	(74.6)	226	(61.5)	1027	(57.8)

Table 1: The total number of medications prescribed and the percentage of medication types filled, as characterised across different patient variables (N=992) (continued).

	Paracetamol n/n filled (%)		NSAIDs n/n filled (%)		Antibiotics n/n filled (%)		Other n/n filled (%)		Total n/n filled (%)	
	684	(51.3)	676	(59.9)	260	(80.4)	569	(61.0)	2189	(59.9)
Discharge day										
Sun (n=120; 12.1%)	93	(46.2)	75	(65.3)	26	(84.6)	43	(58.1)	237	(58.6)
Mon (n=238; 23.4%)	163	(52.1)	150	(57.3)	67	(70.1)	147	(61.2)	527	(58.4)
Tues (n=173; 17.4%)	108	(56.5)	134	(64.9)	56	(89.3)	118	(64.4)	416	(65.9)
Wed (n=127; 12.8%)	89	(47.2)	85	(52.9)	40	(75.0)	70	(62.9)	284	(56.7)
Thurs (n=98; 9.9%)	70	(48.6)	69	(55.1)	21	(76.2)	69	(66.7)	229	(58.5)
Fri (n=120; 12.1%)	88	(47.7)	77	(57.1)	21	(81.0)	66	(42.4)	252	(52.0)
Sat (n=116; 11.7%)	73	(60.3)	86	(65.1)	29	(93.1)	56	(67.9)	244	(67.6)
Discharge time										
2400–0400 (178; 17.9%)	141	(53.9)	137	(55.5)	42	(81.0)	85	(61.2)	405	(58.8)
0400–0800 (111; 11.2%)	78	(48.7)	82	(63.4)	36	(83.3)	55	(63.6)	251	(61.8)
0800–1200 (158; 15.9%)	98	(62.2)	104	(74.0)	49	(77.6)	106	(63.2)	357	(68.1)
1200–1600 (138; 13.9%)	91	(45.1)	106	(60.4)	23	(82.6)	83	(72.3)	303	(60.7)
1600–2000 (212; 21.4%)	145	(47.6)	125	(49.6)	53	(77.4)	137	(51.8)	460	(52.8)
2000–2400 (192; 19.3%)	129	(50.4)	121	(61.2)	57	(82.5)	103	(60.2)	410	(60.5)
Unknown (3; 0.3%)	2	(50.0)	1	(0.0)	0	(0.0)	0	(0.0)	3	(33.3)

[a] MELAA: Middle Eastern, Latin American and African.
[b] Suburb NZDep2013 index: 1 represents areas of least deprived; 10 is most deprived.

GP, although these patient numbers were insufficient to indicate significance.

Medication-level analysis revealed an association between the medication class, number of prescribed items and likelihood of filling a prescription. Other studies have found adherence to be lower in those co-prescribed two or more medications,[6] or that there was no significant difference between number of medications prescribed versus the number of prescriptions filled.[7] Our analysis did not determine whether patients prescribed two or more medications may have been co-prescribed an antibiotic or other high-importance medication, and hence it is not possible to conclude the reasons for the higher rate of filling. It is, however, plausible that patients with more medications are sicker and/or exhibit more severe symptoms and may therefore be more inclined to fill all medications, in comparison to patients with milder and more transient presentations. Furthermore, once patients have presented to a pharmacy with a prescription, they may be more motivated to fill all items.

Paracetamol was the most commonly prescribed item (31.2% of all prescribed medications) and also the least filled prescription (51.3%). Although NSAIDs were prescribed at a similar rate to paracetamol (30.9%), NSAIDs had a significantly higher fill rate (59.9%) in comparison (p<0.01). Analgesics are reported to be some of the more common medications left unused from previous prescriptions, due largely to over-prescribing and/or the patient experiencing adverse effects.[29] Hence it is not uncommon for patients to have a supply of analgesics at home, which they may opt to take rather than filling another prescription. Or patients may make rational decisions to not take analgesics when they no longer seek pain relief.[30,31] It has been proposed that pain relief is a desired health endpoint that health professionals should not attempt to modify.[30] However, assessing the patient's analgesic requirements and questioning them regarding their home supply may help to better optimise analgesic prescribing in EDs.

Unlike analgesics and anti-inflammatories, the failure to take antibiotics can lead to more potentially serious consequences. In this study, antibiotics accounted for 11.9% of prescription items and exhibited a significantly higher fill rate compared with other medications (80.4%, p<0.001). One study reported similar fill rates but found no significant differences between antibiotics and other classes of

Table 2: Univariable analysis comparing medication adherence with total number of medicines and medication types (N=992).

			Percentage filled			
Variable	**Rate ratio**	**95% CI**	**%**	**95% CI**	**Overall P-value**	**Group**
Total meds prescribed						
1	1.00		42.1	(35.2–50.2)	<0.001	a
2	1.32	(1.08–1.61)	55.4	(50.2–61.1)		b
>4	1.41	(1.09–1.84)	59.5	(48.9–72.4)		b c
3	1.59	(1.30–1.94)	66.8	(61.1–73.0)		c
4	1.72	(1.38–2.16)	72.5	(63.3–83.2)		c
Medication type						
Paracetamol	1.00		51.3	(46.2–57.0)	<0.001	a
NSAID	1.17	(1.01–1.35)	59.9	(54.3–66.0)		b
Other	1.19	(1.02–1.38)	61.0	(54.9–67.8)		b
Antibiotic	1.57	(1.32–1.86)	80.4	(70.2–92.1)		c

Table 3: Multivariable analysis comparing medication adherence with age, smoking and number and type of medication (N=992)

					Estimated percentage filled	
Variable	**Level**	**Rate ratio**	**95% CI**	**p-value**	**%**	**95% CI**
Age						
	<10	1.00			64.7	(55.4–75.7)
	10–17	0.64	(0.52–0.80)	<0.001	41.6	(33.3–52.0)
	18–24	0.74	(0.61–0.91)	0.004	48.1	(40.1–57.7)
	25–44	0.83	(0.70–0.97)	0.023	53.6	(46.4–62.0)
	45–64	0.93	(0.79–1.11)	0.426	60.4	(52.2–70.0)
	> 64	1.02	(0.79–1.31)	0.886	65.9	(51.3–84.8)
Smoking						
	No	1.00			62.0	(56.9–67.5)
	Yes	0.79	(0.67–0.93)	0.006	48.9	(41.5–57.7)
	Unknown	0.89	(0.69–1.14)	0.347	54.9	(42.7–70.7)
Total number of medications prescribed						
1	Paracetamol	1.00			20.5	(14.1–29.9)
2		2.25	(1.51–3.33)	<0.001	46.1	(38.2–55.7)
3		2.75	(1.84–4.13)	<0.001	56.5	(46.4–68.8)
4		3.01	(1.87–4.83)	<0.001	61.8	(44.9–84.9)
>4		2.54	(1.34–4.83)	0.004	52.1	(30.5–89.1)
1	NSAID	1.81	(0.98–3.37)	0.060	37.2	(22.2–62.5)
2		2.25	(1.51–3.36)	<0.001	46.1	(37.9–56.3)
3		3.04	(2.05–4.52)	<0.001	62.4	(52.6–74.1)
4		3.35	(2.16–5.19)	<0.001	68.8	(53.3–88.7)
>4		3.06	(1.74–5.37)	<0.001	62.8	(40.7–97.0)
1	Antibiotic	3.13	(1.97–4.99)	<0.001	64.3	(47.2–87.8)
2		3.46	(2.20–5.46)	<0.001	71.1	(52.8–95.8)
3		3.50	(2.29–5.34)	<0.001	71.7	(56.4–91.2)
4		3.40	(2.00–5.77)	<0.001	69.7	(46.9–103.5)
>4		4.48	(2.32–8.68)	<0.001	92.1	(52.6–161.1)
1	Other	1.79	(1.09–2.96)	0.022	36.8	(25.9–52.3)
2		2.49	(1.63–3.80)	<0.001	51.1	(40.4–64.7)
3		2.96	(1.98–4.44)	<0.001	60.8	(49.6–74.6)
4		3.42	(2.21–5.27)	<0.001	70.1	(54.2–90.6)
>4		2.33	(1.47–3.69)	<0.001	47.8	(35.6–64.0)

medication,[31] whereas other studies have found that oral anti-infective agents exhibit the lowest rates of primary medication non-adherence.[4–6] These discrepancies are likely due to the varying methods of dispensing antibiotics in ED studies: for example, some were dispensed in the form of a fully-paid prescription, and in others as a starter pack with instructions for a follow-on prescription.[18] Although in our study there were no patient factors that significantly affected antibiotic filling, there was some indication to suggest that age, ethnicity and access to a regular GP may be associated with primary medication non-adherence.

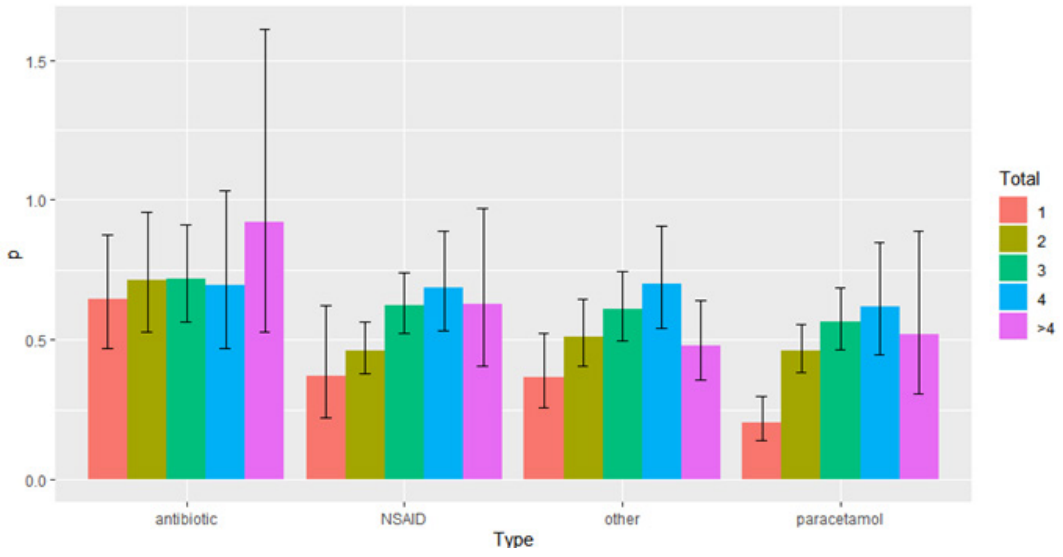
Several strategies to improve antibiotic filling rates in EDs have yielded variable results. Patients who were dispensed antibiotics directly from an ED tended to have better adherence than patients issued with a prescription, even if their prescription had been fully paid for.[18] Previous studies have reported that, once patients fill their prescriptions and get into a routine, they are more likely to continue taking their antibiotics;[30] for those who do not fill their prescriptions, commonly reported reasons were cost, lack of transportation and being busy.[30] It has also been suggested that patients who are discharged during pharmacy opening hours may be more likely to fill their prescriptions,[18] but discharge day and time was not seen to influence filling in our study.

Limitations

This study was conducted at a single ED site (CMH-ED), and given the small cohort and patient demographic at CMH-ED, it may not be possible to generalise the results to other EDs across New Zealand. Sampling of the study population was obtained from consecutive patients over a period of four weeks, which may have contributed to selection bias. As primary medication non-adherence is influenced by a multitude of factors, including ED-system factors, access to a dispensing pharmacy, patient social and psychological influences and financial support, many of these factors could not be determined using a retrospective method. Moreover, it could not be determined whether patients had an existing supply of medicine at home, experienced symptom resolution and no longer required analgesics, or were provided with a 'back-pocket prescription' (ie, 'just in case' prescribing) that was no longer required, resulting in unfilled prescription medications. Additionally, patients could not be assessed for possible medication adverse effects over time, and readmission rates due to non-adherence were not assessed.

Since medication adherence was inferred from a prescription being filled, true nonadherence rates are likely to be under-

Figure 1: Percentage (p) of medication types filled compared with number of items prescribed. Black lines indicate confidence intervals.



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estimated. TestSafe™ displayed only those prescriptions that had been entered into the system, but it did not indicate whether the medication had been collected or taken by the patient. Telephoning patients several months after ED discharge to confirm medical records could have resulted in recall bias. With two of 15 patients having reported conflicting dispensing records, it suggests that the system may have a fairly substantial error rate. These differences, however, could also be based on inaccurate recall or biased by social desirability. Moreover, admission records for CMH-ED patients were not always accurate or complete. In busy EDs, these are often written under time constraints and personal information is mainly obtained through patient self-reporting.

Conclusions

In this study, age, smoking and number of prescribed medications were predictors of non-adherence to antibiotics and analgesics. Since this study, changes have been made to the New Zealand prescription co-payment structure and free paediatric prescriptions have been extended to 13-year-olds. There are also a growing number of discount pharmacies offering free prescriptions for all patients. With the cost of medication affecting the ability of some patients to fill their prescriptions, free prescriptions may ease the financial burden for people who are unable to afford co-payments and improve treatment opportunities, and further research is warranted to determine whether these changes have any notable effects on the rates of non-adherence in the ED. More work is required to identify patients likely to be non-adherent and enlist available resources to reduce barriers to adherence. Hospital discharge may be the best time at which to communicate medication treatments and emphasise medication adherence.

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Appendix

Appendix Table 1: Bivariable analysis of paracetamol (N=992).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR [a]	RR lower 95	RR upper 95	p-value	Group
Gender										
Male	189	359	52.6%	45.6%	60.7%	1.00				a
Female	162	325	49.8%	42.7%	58.2%	0.95	0.77	1.17	0.610	a
Age										
< 1	135	233	57.9%	48.9%	68.6%	1.00				a
10-17	30	89	33.7%	23.6%	48.2%	0.58	0.39	0.86	0.007	b
18-24	30	82	36.6%	25.6%	52.3%	0.63	0.43	0.94	0.023	b
25-44	77	151	51.0%	40.8%	63.8%	0.88	0.67	1.16	0.371	a b
45-64	63	107	58.9%	46.0%	75.4%	1.02	0.75	1.37	0.916	a
> 64	16	22	72.7%	44.5%	118.8%	1.26	0.75	2.11	0.390	a
Ethnicity										
NZ European	74	138	53.6%	42.7%	67.4%	1.00				a b
Asian	61	111	55.0%	42.8%	70.6%	1.02	0.73	1.44	0.887	a b
MELAA[b]	11	12	91.7%	50.7%	165.6%	1.71	0.91	3.22	0.097	a
Māori	53	128	41.4%	31.6%	54.2%	0.77	0.54	1.10	0.151	b
Pacific	150	290	51.7%	44.1%	60.7%	0.96	0.73	1.27	0.800	a b
Unknown	2	5	40.0%	10.0%	160.1%	0.75	0.18	3.04	0.683	a b
Country of Birth										
NZ	223	461	48.4%	42.4%	55.2%	1.00				a
Outside NZ	109	189	57.7%	47.8%	69.6%	1.19	0.95	1.50	0.132	a
Unknown	19	34	55.9%	35.6%	87.6%	1.16	0.72	1.85	0.546	a
Suburb Deprivation [c]										
1	4	7	57.1%	21.4%	152.4%	1.00				a
2	6	13	46.2%	20.7%	102.8%	0.81	0.23	2.86	0.741	a
3	5	10	50.0%	20.8%	120.2%	0.88	0.23	3.26	0.842	a
4	23	35	65.7%	43.7%	98.9%	1.15	0.40	3.33	0.796	a
5	8	12	66.7%	33.3%	133.4%	1.17	0.35	3.87	0.801	a
6	15	25	60.0%	36.2%	99.6%	1.05	0.35	3.16	0.931	a
7	16	29	55.2%	33.8%	90.1%	0.97	0.32	2.89	0.950	a
8	10	18	55.6%	29.9%	103.3%	0.97	0.30	3.10	0.962	a
9	117	259	45.2%	37.7%	54.2%	0.79	0.29	2.14	0.644	a
10	146	273	53.5%	45.5%	62.9%	0.94	0.35	2.53	0.896	a
Unknown	1	3	33.3%	4.7%	236.9%	0.58	0.07	5.22	0.630	a

Appendix Table 1: Bivariable analysis of paracetamol (N=992) (continued).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR [a]	RR lower 95	RR upper 95	p-value	Group
Language										
English	309	604	51.2%	45.8%	57.2%	1.00				a
Non-English	24	43	55.8%	37.4%	83.3%	1.09	0.72	1.65	0.681	a
Unknown	18	37	48.6%	30.6%	77.2%	0.95	0.59	1.53	0.836	a
Occupation										
Student	73	162	45.1%	35.8%	56.7%	0.01				a
Unemployed	17	47	36.2%	22.5%	58.2%	1.00	0.47	1.36	0.414	a
Homemaker	15	41	36.6%	22.0%	60.7%	0.81	0.47	1.42	0.462	a
Retired	13	20	65.0%	37.7%	112.0%	1.44	0.80	2.60	0.224	a
Other	74	125	59.2%	47.1%	74.4%	1.31	0.95	1.82	0.098	a
Employed	49	100	49.0%	37.0%	64.8%	1.09	0.76	1.56	0.650	a
Infant/child	102	175	58.3%	48.0%	70.8%	1.29	0.96	1.75	0.093	a
Unknown	8	14	57.1%	28.6%	114.3%	1.27	0.61	2.63	0.524	a
Regular GP										
Yes	340	662	51.4%	46.2%	57.1%	1.00				a
No	11	22	50.0%	27.7%	90.3%	0.97	0.53	1.77	0.930	a
Smoking										
No	301	557	54.0%	48.3%	60.5%	1.00				a
Yes	33	93	35.5%	25.2%	49.9%	0.66	0.46	0.94	0.022	b
Unknown	17	34	50.0%	31.1%	80.5%	0.93	0.57	1.51	0.755	a b
Items prescribed										
1	30	121	24.8%	17.3%	35.5%	1.00				a
2	145	278	52.2%	44.3%	61.4%	2.10	1.42	3.12	0.000	b
3	120	197	60.9%	50.9%	72.9%	2.46	1.65	3.67	0.000	b
4	42	63	66.7%	49.3%	90.2%	2.69	1.68	4.30	0.000	b
>4	14	25	56.0%	33.2%	94.6%	2.26	1.20	4.26	0.012	b
Discharge month										
Autumn	184	339	54.3%	47.0%	62.7%	1.00				a
Winter	167	345	48.4%	41.6%	56.3%	0.89	0.72	1.10	0.284	a

Appendix Table 1: Bivariable analysis of paracetamol (N=992) (continued).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR[a]	RR lower 95	RR upper 95	p-value	Group
Discharge Day										
Sun	43	93	46.2%	34.3%	62.4%	1.00				a
Mon	85	163	52.1%	42.2%	64.5%	1.13	0.78	1.63	0.520	a
Tues	61	108	56.5%	43.9%	72.6%	1.22	0.83	1.80	0.315	a
Wed	42	89	47.2%	34.9%	63.9%	1.02	0.67	1.56	0.925	a
Thurs	34	70	48.6%	34.7%	68.0%	1.05	0.67	1.65	0.830	a
Fri	42	88	47.7%	35.3%	64.6%	1.03	0.67	1.58	0.884	a
Sat	44	73	60.3%	44.8%	81.0%	1.30	0.86	1.98	0.216	a
Discharge Time										
2400-0400	76	141	53.9%	43.0%	67.5%	1.00				a
0400-0800	38	78	48.7%	35.4%	67.0%	0.90	0.61	1.33	0.611	a
0800-1200	61	98	62.2%	48.4%	80.0%	1.15	0.82	1.62	0.402	a
1200-1600	41	91	45.1%	33.2%	61.2%	0.84	0.57	1.22	0.355	a
1600-2000	69	145	47.6%	37.6%	60.3%	0.88	0.64	1.22	0.454	a
2000-2400	65	129	50.4%	39.5%	64.3%	0.93	0.67	1.30	0.690	a
Unknown	1	2	50.0%	7.0%	355.4%	0.93	0.13	6.67	0.941	a

[a] RR: Rate ratio
[b] MELAA: Middle Eastern, Latin American and African
[c] Suburb deprivation: 1 represents areas of least deprived; 10 is most deprived.

Appendix Table 2: Bivariable analysis of nonsteroidal anti-inflammatory drugs (N=992).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR[a]	RR lower 95	RR upper 95	p-value	Group
Gender										
Male	233	370	63.0%	55.4%	71.6%	1.00				a
Female	172	306	56.2%	48.4%	65.3%	0.89	0.73	1.09	0.258	a
Age										
< 10	81	120	67.5%	54.3%	83.9%	1.00				b c
10-17	39	87	44.8%	32.7%	61.4%	0.66	0.45	0.97	0.036	a
18-24	57	114	50.0%	38.6%	64.8%	0.74	0.53	1.04	0.083	a b
25-44	115	196	58.7%	48.9%	70.4%	0.87	0.65	1.16	0.334	a b c
45-64	99	139	71.2%	58.5%	86.7%	1.06	0.79	1.42	0.720	c
> 64	14	20	70.0%	41.4%	118.2%	1.04	0.59	1.83	0.900	a b c
Ethnicity										
NZ European	100	156	64.1%	52.7%	78.0%	1.00				a b
Asian	74	123	60.2%	47.9%	75.6%	0.94	0.69	1.27	0.679	a b
MELAA[b]	12	13	92.3%	52.4%	162.6%	1.44	0.79	2.62	0.233	a
Māori	62	127	48.8%	38.1%	62.6%	0.76	0.55	1.05	0.092	b
Pacific	154	252	61.1%	52.2%	71.6%	0.95	0.74	1.23	0.710	a b
Unknown	3	5	60.0%	19.3%	186.2%	0.94	0.30	2.95	0.910	a b
Country of Birth										
NZ	226	413	54.7%	48.0%	62.3%	1.00				a
Outside NZ	155	225	68.9%	58.8%	80.6%	1.26	1.03	1.54	0.027	b
Unknown	24	38	63.2%	42.3%	94.3%	1.15	0.76	1.76	0.504	a b
Suburb Deprivation[c]										
1	8	11	72.7%	36.4%	145.5%	1.00				a
2	11	22	50.0%	27.7%	90.3%	0.69	0.28	1.71	0.420	a
3	10	13	76.9%	41.4%	143.0%	1.06	0.42	2.68	0.906	a
4	25	39	64.1%	43.3%	94.9%	0.88	0.40	1.95	0.756	a
5	9	13	69.2%	36.0%	133.1%	0.95	0.37	2.47	0.919	a
6	18	29	62.1%	39.1%	98.5%	0.85	0.37	1.96	0.709	a
7	20	29	69.0%	44.5%	106.9%	0.95	0.42	2.15	0.899	a
8	10	16	62.5%	33.6%	116.2%	0.86	0.34	2.18	0.749	a
9	128	235	54.5%	45.8%	64.8%	0.75	0.37	1.53	0.428	a
10	165	267	61.8%	53.0%	72.0%	0.85	0.42	1.73	0.653	a
Unknown	1	2	50.0%	7.0%	355.4%	0.69	0.09	5.50	0.724	a

Appendix Table 2: Bivariable analysis of nonsteroidal anti-inflammatory drugs (N=992) (continued).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR [a]	RR lower 95	RR upper 95	p-value	Group
Language										
English	367	612	60.0%	54.1%	66.4%	1.00				a
Non-English	19	31	61.3%	39.1%	96.1%	1.02	0.64	1.62	0.926	a
Unknown	19	33	57.6%	36.7%	90.3%	0.96	0.61	1.52	0.863	a
Occupation										
Student	80	144	55.6%	44.6%	69.2%	1.00				a b
Unemployed	30	64	46.9%	32.8%	67.1%	0.84	0.55	1.28	0.427	a b
Homemaker	18	45	40.0%	25.2%	63.5%	0.72	0.43	1.20	0.208	a
Retired	10	16	62.5%	33.6%	116.2%	1.12	0.58	2.17	0.725	a b
Other	116	173	67.1%	55.9%	80.4%	1.21	0.91	1.60	0.196	b
Employed	79	126	62.7%	50.3%	78.2%	1.13	0.83	1.54	0.446	a b
Infant/child	60	90	66.7%	51.8%	85.9%	1.20	0.86	1.68	0.286	a b
Unknown	12	18	66.7%	37.8%	117.4%	1.20	0.65	2.20	0.556	a b
Regular GP										
Yes	395	654	60.4%	54.7%	66.7%	1.00				a
No	10	22	45.5%	24.4%	84.5%	0.75	0.40	1.41	0.375	a
Smoking										
No	315	511	61.6%	55.2%	68.8%	1.00				a
Yes	68	123	55.3%	43.6%	70.1%	0.90	0.69	1.17	0.416	a
Unknown	22	42	52.4%	34.5%	79.6%	0.85	0.55	1.31	0.460	a
Items prescribed										
1	15	35	42.9%	25.8%	71.1%	1.00				a b
2	127	248	51.2%	43.0%	60.9%	1.19	0.70	2.04	0.514	b
3	170	261	65.1%	56.0%	75.7%	1.52	0.90	2.58	0.120	a
4	71	100	71.0%	56.3%	89.6%	1.66	0.95	2.89	0.076	a
>4	22	32	68.8%	45.3%	104.4%	1.60	0.83	3.09	0.158	a b
Discharge month										
Autumn	211	346	61.0%	53.3%	69.8%	1.00				a
Winter	194	330	58.8%	51.1%	67.7%	0.96	0.79	1.17	0.713	a

Appendix Table 2: Bivariable analysis of nonsteroidal anti-inflammatory drugs (N=992) (continued).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR [a]	RR lower 95	RR upper 95	p-value	Group
Discharge Day										
Sun	49	75	65.3%	49.4%	86.5%	1.00				a
Mon	86	150	57.3%	46.4%	70.8%	0.88	0.62	1.25	0.466	a
Tues	87	134	64.9%	52.6%	80.1%	0.99	0.70	1.41	0.972	a
Wed	45	85	52.9%	39.5%	70.9%	0.81	0.54	1.21	0.308	a
Thurs	38	69	55.1%	40.1%	75.7%	0.84	0.55	1.29	0.429	a
Fri	44	77	57.1%	42.5%	76.8%	0.87	0.58	1.31	0.519	a
Sat	56	86	65.1%	50.1%	84.6%	1.00	0.68	1.46	0.986	a
Discharge Time										
2400-0400	76	137	55.5%	44.3%	69.5%	1.00				a b
0400-0800	52	82	63.4%	48.3%	83.2%	1.14	0.80	1.63	0.457	a b
0800-1200	77	104	74.0%	59.2%	92.6%	1.33	0.97	1.83	0.074	a
1200-1600	64	106	60.4%	47.2%	77.2%	1.09	0.78	1.52	0.618	a b
1600-2000	62	125	49.6%	38.7%	63.6%	0.89	0.64	1.25	0.513	b
2000-2400	74	121	61.2%	48.7%	76.8%	1.10	0.80	1.52	0.550	a b
Unknown	0	1	0.0%	0.0%	Inf	0.00	0.00	Inf	0.978	a b

[a] RR: Rate ratio
[b] MELAA: Middle Eastern, Latin American and African
[c] Suburb deprivation: 1 represents areas of least deprived; 10 is most deprived.

Appendix Table 3: Bivariable analysis of antibiotics (N=992).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR[a]	RR lower 95	RR upper 95	p-value	Group
Gender										
Male	100	124	80.6%	66.3%	98.1%	1.00				a
Female	109	136	80.1%	66.4%	96.7%	0.99	0.76	1.30	0.964	a
Age										
< 10	82	97	84.5%	68.1%	105.0%	1.00				a
10-17	14	22	63.6%	37.7%	107.5%	0.75	0.43	1.33	0.326	a
18-24	24	31	77.4%	51.9%	115.5%	0.92	0.58	1.44	0.705	a
25-44	42	51	82.4%	60.8%	111.5%	0.97	0.67	1.41	0.890	a
45-64	33	44	75.0%	53.3%	105.5%	0.89	0.59	1.33	0.562	a
> 64	14	15	93.3%	55.3%	157.6%	1.10	0.63	1.95	0.732	a
Ethnicity										
NZ European	48	52	92.3%	69.5%	122.5%	1.00				a
Asian	25	34	73.5%	49.7%	108.8%	0.80	0.49	1.29	0.356	a
MELAA[b]	3	3	100.0%	32.2%	310.3%	1.08	0.34	3.48	0.893	a
Māori	35	49	71.4%	51.3%	99.5%	0.77	0.50	1.20	0.249	a
Pacific	98	122	80.3%	65.9%	97.9%	0.87	0.62	1.23	0.430	a
Unknown	0	0		16.4%	288.8%	0.75	0.18	3.04	0.683	a
Country of Birth										
NZ	140	177	79.1%	67.0%	93.4%	1.00				a
Outside NZ	62	75	82.7%	64.4%	106.0%	1.05	0.78	1.41	0.772	a
Unknown	7	8	87.5%	41.7%	183.6%	1.11	0.52	2.36	0.794	a
Suburb Deprivation[c]										
1	0	0		9.0%	3249.0	1.00				a
2	1	3	33.3%	4.7%	236.9%	0.19	0.01	6.66	0.364	a
3	5	5	100.0%	41.6%	240.4%	0.58	0.03	12.54	0.731	a
4	8	9	88.9%	44.4%	177.8%	0.52	0.03	10.63	0.670	a
5	5	6	83.3%	34.7%	200.3%	0.49	0.02	10.45	0.645	a
6	11	15	73.3%	40.6%	132.5%	0.43	0.02	8.58	0.579	a
7	6	6	100.0%	44.9%	222.7%	0.58	0.03	12.28	0.729	a
8	5	6	83.3%	34.7%	200.3%	0.49	0.02	10.45	0.645	a
9	78	104	75.0%	60.1%	93.6%	0.44	0.02	8.34	0.583	a
10	89	105	84.8%	68.9%	104.3%	0.49	0.03	9.42	0.640	a
Unknown	1	1	100.0%	14.1%	710.9%	0.58	0.07	5.22	0.630	a

Appendix Table 3: Bivariable analysis of antibiotics (N=992) (continued).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR [a]	RR lower 95	RR upper 95	p-value	Group
Language										
English	186	230	80.9%	70.0%	93.4%	1.00				a
Non-English	10	13	76.9%	41.4%	143.0%	0.95	0.50	1.80	0.878	a
Unknown	13	17	76.5%	44.4%	131.7%	0.95	0.54	1.66	0.845	a
Occupation										
Student	49	61	80.3%	60.7%	106.3%	1.00				a
Unemployed	14	19	73.7%	43.6%	124.5%	0.92	0.51	1.66	0.776	a
Homemaker	11	19	57.9%	32.0%	104.6%	0.72	0.37	1.39	0.326	a
Retired	13	14	92.9%	53.9%	160.0%	1.16	0.63	2.13	0.642	a
Other	38	43	88.4%	64.3%	121.5%	1.10	0.72	1.68	0.659	a
Employed	29	37	78.4%	54.5%	112.8%	0.98	0.62	1.54	0.916	a
Infant/child	52	62	83.9%	63.9%	110.1%	1.04	0.71	1.54	0.828	a
Unknown	3	5	60.0%	19.3%	186.2%	0.75	0.23	2.40	0.624	a
Regular GP										
Yes	203	249	81.5%	71.0%	93.6%	1.00				a
No	6	11	54.5%	24.5%	121.5%	0.67	0.30	1.51	0.332	a
Smoking										
No	164	200	82.0%	70.4%	95.6%	1.00				a
Yes	36	48	75.0%	54.1%	104.0%	0.91	0.64	1.31	0.628	a
Unknown	9	12	75.0%	39.0%	144.2%	0.91	0.47	1.79	0.794	a
Items prescribed										
1	44	56	78.6%	58.5%	105.6%	1.00				a
2	49	58	84.5%	63.8%	111.8%	1.08	0.72	1.62	0.727	a
3	77	96	80.2%	64.1%	100.3%	1.02	0.70	1.48	0.913	a
4	26	37	70.3%	47.8%	103.2%	0.89	0.55	1.45	0.652	a
>4	13	13	100.0%	58.0%	172.3%	1.27	0.69	2.36	0.445	a
Discharge month										
Autumn	115	134	85.8%	71.5%	103.0%	1.00				a
Winter	94	126	74.6%	60.9%	91.3%	0.87	0.66	1.14	0.314	a

Appendix Table 3: Bivariable analysis of antibiotics (N=992) (continued).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR [a]	RR lower 95	RR upper 95	p-value	Group
Discharge Day										
Sun	22	26	84.6%	55.7%	128.5%	1.00				a
Mon	47	67	70.1%	52.7%	93.4%	0.83	0.50	1.38	0.468	a
Tues	50	56	89.3%	67.7%	117.8%	1.06	0.64	1.74	0.834	a
Wed	30	40	75.0%	52.4%	107.3%	0.89	0.51	1.54	0.667	a
Thurs	16	21	76.2%	46.7%	124.4%	0.90	0.47	1.71	0.750	a
Fri	17	21	81.0%	50.3%	130.3%	0.96	0.51	1.80	0.891	a
Sat	27	29	93.1%	63.8%	135.8%	1.10	0.63	1.93	0.739	a
Discharge Time										
2400-0400	34	42	81.0%	57.8%	113.3%	1.00				a
0400-0800	30	36	83.3%	58.3%	119.2%	1.03	0.63	1.68	0.908	a
0800-1200	38	49	77.6%	56.4%	106.6%	0.96	0.60	1.52	0.856	a
1200-1600	19	23	82.6%	52.7%	129.6%	1.02	0.58	1.79	0.944	a
1600-2000	41	53	77.4%	56.9%	105.1%	0.96	0.61	1.51	0.845	a
2000-2400	47	57	82.5%	61.9%	109.8%	1.02	0.66	1.58	0.935	a
Unknown	0	0		10.1%	556.3%	0.93	0.13	6.67	0.941	a

[a] RR: Rate ratio
[b] MELAA: Middle Eastern, Latin American and African
[c] Suburb deprivation: 1 represents areas of least deprived; 10 is most deprived.

Appendix Table 4: Bivariable analysis of other medication (N=992).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR [a]	RR lower 95	RR upper 95	p-value	Group
Gender										
Male	160	251	63.7%	54.6%	74.4%	1.00				a
Female	187	318	58.8%	50.9%	67.9%	0.92	0.75	1.14	0.454	a
Age										
< 10	88	129	68.2%	55.3%	84.1%	1.00				a
10-17	22	44	50.0%	32.9%	76.0%	0.73	0.46	1.17	0.192	a
18-24	40	69	58.0%	42.5%	79.0%	0.85	0.58	1.23	0.393	a
25-44	83	145	57.2%	46.2%	71.0%	0.84	0.62	1.13	0.252	a
45-64	81	128	63.3%	50.9%	78.7%	0.93	0.69	1.25	0.626	a
> 64	33	54	61.1%	43.4%	86.0%	0.90	0.60	1.34	0.590	a
Ethnicity										
NZ European	76	119	63.9%	51.0%	80.0%	1.00				a
Asian	56	86	65.1%	50.1%	84.6%	1.02	0.72	1.44	0.912	a
MELAA [b]	4	8	50.0%	18.8%	133.3%	0.78	0.29	2.14	0.633	a
Māori	61	107	57.0%	44.3%	73.3%	0.89	0.64	1.25	0.509	a
Pacific	147	246	59.8%	50.8%	70.2%	0.94	0.71	1.23	0.638	a
Unknown	3	3	100.0%	32.2%	310.3%	1.57	0.49	4.96	0.446	a
Country of Birth										
NZ	209	332	63.0%	55.0%	72.1%	1.00				a
Outside NZ	118	197	59.9%	50.0%	71.8%	0.95	0.76	1.19	0.666	a
Unknown	20	40	50.0%	32.2%	77.5%	0.79	0.50	1.26	0.325	a
Suburb Deprivation [c]										
1	2	3	66.7%	16.7%	266.8%	1.00				a
2	4	9	44.4%	16.7%	118.5%	0.67	0.12	3.64	0.640	a
3	2	4	50.0%	12.5%	200.1%	0.75	0.11	5.32	0.774	a
4	13	20	65.0%	37.7%	112.0%	0.97	0.22	4.32	0.973	a
5	9	9	100.0%	52.0%	192.3%	1.50	0.32	6.94	0.604	a
6	24	32	75.0%	50.3%	111.9%	1.12	0.27	4.76	0.873	a
7	9	12	75.0%	39.0%	144.2%	1.12	0.24	5.21	0.880	a
8	5	11	45.5%	18.9%	109.3%	0.68	0.13	3.51	0.647	a
9	135	211	64.0%	54.0%	75.7%	0.96	0.24	3.88	0.954	a
10	142	253	56.1%	47.6%	66.2%	0.84	0.21	3.40	0.809	a
Unknown	2	5	40.0%	10.0%	160.1%	0.60	0.08	4.26	0.609	a

Appendix Table 4: Bivariable analysis of other medication (N=992) (continued).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR [a]	RR lower 95	RR upper 95	p-value	Group
Language										
English	313	520	60.2%	53.9%	67.2%	1.00				a
Non-English	22	30	73.3%	48.3%	111.4%	1.22	0.79	1.88	0.371	a
Unknown	12	19	63.2%	35.9%	111.3%	1.05	0.59	1.87	0.870	a
Occupation										
Student	65	113	57.5%	45.1%	73.4%	1.00				a
Unemployed	28	60	46.7%	32.2%	67.6%	0.81	0.52	1.26	0.355	a
Homemaker	25	46	54.3%	36.7%	80.5%	0.94	0.60	1.50	0.809	a
Retired	28	47	59.6%	41.1%	86.3%	1.04	0.66	1.61	0.877	a
Other	76	109	69.7%	55.7%	87.3%	1.21	0.87	1.69	0.255	a
Employed	56	99	56.6%	43.5%	73.5%	0.98	0.69	1.41	0.927	a
Infant/child	60	85	70.6%	54.8%	90.9%	1.23	0.86	1.74	0.253	a
Unknown	9	10	90.0%	46.8%	173.0%	1.56	0.78	3.14	0.208	a
Regular GP										
Yes	338	552	61.2%	55.0%	68.1%	1.00				a
No	9	17	52.9%	27.5%	101.8%	0.86	0.45	1.68	0.667	a
Smoking										
No	281	437	64.3%	57.2%	72.3%	1.00				a
Yes	47	102	46.1%	34.6%	61.3%	0.72	0.53	0.98	0.034	b
Unknown	19	30	63.3%	40.4%	99.3%	0.98	0.62	1.57	0.949	a b
Items prescribed										
1	33	78	42.3%	30.1%	59.5%	1.00				a
2	80	140	57.1%	45.9%	71.2%	1.35	0.90	2.03	0.146	a b
3	116	169	68.6%	57.2%	82.3%	1.62	1.10	2.39	0.014	b c
4	67	84	79.8%	62.8%	101.4%	1.89	1.24	2.86	0.003	c
>4	51	98	52.0%	39.5%	68.5%	1.23	0.79	1.91	0.354	a b
Discharge month										
Autumn	208	343	60.6%	52.9%	69.5%	1.00				a
Winter	139	226	61.5%	52.1%	72.6%	1.01	0.82	1.26	0.897	a

Appendix Table 4: Bivariable analysis of other medication (N=992) (continued).

Variable	Total filled	Total prescribed	% filled	% lower 95	% upper 95	RR[a]	RR lower 95	RR upper 95	p-value	Group
Discharge Day										
Sun	25	43	58.1%	39.3%	86.1%	1.00				a
Mon	90	147	61.2%	49.8%	75.3%	1.05	0.68	1.64	0.819	a
Tues	76	118	64.4%	51.4%	80.7%	1.11	0.71	1.74	0.657	a
Wed	44	70	62.9%	46.8%	84.5%	1.08	0.66	1.77	0.755	a
Thurs	46	69	66.7%	49.9%	89.0%	1.15	0.70	1.87	0.582	a
Fri	28	66	42.4%	29.3%	61.5%	0.73	0.43	1.25	0.252	a
Sat	38	56	67.9%	49.4%	93.3%	1.17	0.70	1.93	0.548	a
Discharge Time										
2400-0400	52	85	61.2%	46.6%	80.3%	1.00				a
0400-0800	35	55	63.6%	45.7%	88.7%	1.04	0.68	1.60	0.857	a
0800-1200	67	106	63.2%	49.7%	80.3%	1.03	0.72	1.48	0.860	a
1200-1600	60	83	72.3%	56.1%	93.1%	1.18	0.82	1.71	0.378	a
1600-2000	71	137	51.8%	41.1%	65.4%	0.85	0.59	1.21	0.363	a
2000-2400	62	103	60.2%	46.9%	77.2%	0.98	0.68	1.42	0.931	a
Unknown	0	0		7.7%	416.3%	0.93	0.13	6.67	0.941	a

[a] RR: Rate ratio
[b] MELAA: Middle Eastern, Latin American and African
[c] Suburb deprivation: 1 represents areas of least deprived; 10 is most deprived.

Competing interests:
Nil.
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Complications of endoscopically placed duodenal stents for malignant duodenal outlet obstruction

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ABSTRACT

BACKGROUND: Endoscopically placed duodenal stents are commonly performed procedures for palliation of obstruction due to malignancy. A relatively small number of studies highlight the potential complications of this procedure, and to date no data have been published in New Zealand specifically addressing this issue. We aimed to retrospectively review complications from duodenal stents at our center and factors associated with the complications.

METHOD: We retrospectively reviewed our endoscopy reporting system, Provation MD, for patients who underwent endoscopic duodenal stenting between 1 April 2010 and 31 March 2020. We searched the system for the keywords 'prosthesis or stent', 'duodenal mass or tumour' and 'duodenal stenosis or stricture'. Their clinical records were reviewed. Patients were included if they had a duodenal stent inserted to relieve a malignant duodenal obstruction. Patients were excluded if the obstruction was due to a benign pathology or if the obstruction was proximal to duodenum. Patient demographics, the type of stent used and any stent-related complications were recorded. Previous radiotherapy to chest or abdomen was also recorded.

RESULTS: We identified 61 patients who underwent palliative endoscopic duodenal stenting. The overall complication rate was 15% (9/61), with five cases of stent migration, two cases of perforation and two cases of late tumour ingrowth requiring re-stenting. Three out of five stent-migration cases had non-obstructive lesions. Both the cases of perforation had previous radiotherapy.

CONCLUSION: Duodenal stenting can be performed safely in most patients with malignant duodenal obstruction. The complication rate was found to be higher among the 60–69 age group, the New Zealand Māori/Pacific Islander ethnic group, patients with Niti-S stent and those with duodenal adenocarcinoma as the primary diagnosis, but these higher rates were not found to be statistically significant. Larger studies are required to assess factors associated with complication rates.

Malignant duodenal stenosis is a common presentation of inoperable metastatic pancreatic cancer. It can be observed in up to 15% of patients.[1,2] Inoperable primary duodenal and biliary cancers, along with lymphoma and metastatic spread of other malignancies, are other common causes of duodenal obstruction.[3,4] Common symptoms are abdominal pain, nausea, vomiting and weight loss, which significantly impact quality of life.[5] Often these patients are old with comorbidities and have advanced disease, and their median term of survival is only 3–6 months.[6] This precludes any definitive or even palliative surgical intervention because <40% of these patients are fit to undergo a surgical procedure.[7]

Duodenal stenting effectively relieves obstruction and is relatively less invasive in comparison to surgical interventions like gastroenterostomy.[8] Previous studies have shown that, in comparison to surgical therapy, endoscopic stenting significantly reduces length of stay post procedure and time to commencing free oral fluids and light diet.[9] However, the data in terms

of safety of the procedure are lacking. Commonly reported complications of duodenal stenting in the literature are bleeding, perforation, pancreatitis and stent migration.[2,10,11] Previous radiotherapy is considered a risk factor for perforation post stenting in the upper gastrointestinal (GI) tract.[12]

The aim of this study was to review the complication rates of endoscopically placed duodenal stents for malignant duodenal obstruction and to determine factors associated with the complications.

Patients and methods

All patients who underwent duodenal stenting for malignant duodenal obstruction between 1 April 2010 and 31 of March 2020 at Middlemore Hospital in Auckland were identified by searching Provation MD database. All the endoscopic procedures at our center are reported using Provation MD, which is maintained by the department of gastroenterology. We searched for the keywords 'prosthesis or stent', 'duodenal mass or tumour' and 'duodenal stenosis or stricture'. We reviewed the records of all patients who were positive for any of the criteria and then collated the database of patients who had palliative duodenal stenting for malignant duodenal obstruction.

Definitive surgery was contraindicated in these patients either due to advanced metastatic disease, lesions that were not resectable or significant patient comorbidities.

Patients were included if they had a duodenal stent inserted to relieve a malignant duodenal obstruction.

Patients were excluded if the obstruction was due to a benign pathology. Patients with gastric-outlet obstruction were also excluded, as the aim of this study was specifically to study the complications of duodenal stents.

The data collected for each patient included age, gender, ethnicity, cause of the malignant duodenal obstruction, any complications associated with the stent, history of previous radiotherapy treatment and type of stent used.

Technical and clinical success of the stent was analysed as well. Technical success was defined as satisfactory positioning of the stent endoscopically and radiologically. Clinical success was defined as improvement in patient symptoms at the time of discharge or during outpatient clinic assessment post stent insertion.

Ethics approval was obtained for this study.

Data analysis

The data were analysed descriptively in terms of counts and proportions for categorical variables and means, with standard deviation for continuous variables. The complication rates are reported with 95% confidence intervals. Chi-square and fisher exact tests were carried out to test for a significant association in terms of the risk factors and complication rates. A p-value of less than 5% was considered as statistically significant.

Results

Between 1 April 2010 and 31 March 2020, 61 patients underwent palliative duodenal stenting. Median age was 65 years (range 40–96). There were 32 males and 29 female patients. Almost 40% of the patients were New Zealand European. All 61 cases of stenting were technically successful and all cases but one were clinically successful (Table 1).

Pancreatic adenocarcinoma causing duodenal obstruction was the most common indication for palliative duodenal stenting during the study period (52%). This was followed by duodenal adenocarcinoma (21%). The 'others' category included four cases of metastatic colorectal carcinoma, three of gastric adenocarcinoma, two of metastatic renal cell carcinoma and one each of duodenal neuroendocrine tumour, metastatic cervical squamous cell carcinoma and small cell type extra-pulmonary neuroendocrine tumour (Figure 1).

Niti-S stent (TaeWoong) was the most commonly used stent (69%) during the study period, as shown in Figure 2.

Most cases (85%) had no complications. The complication rate was 15% with 95% confidence interval (5.9%, 23.7%). Out of the nine cases with complications (Table 2), five were stent migration, two were perforation and two were tumour ingrowth requiring

re-stenting. Three out of the five stent migrations had non-obstructive lesions. Both the perforation cases had previous radiotherapy. Both cases of tumour ingrowth were late (>28 days) complications.

Table 2: Number of cases with or without complication and the type of complication involved.

Complications	N
No	52
Yes	9
Migration	5
Perforation Tumour ingrowth	2 2

Figures 3–6 show the percentage of complications associated with age group, ethnicity, stent type and primary diagnosis.

Discussion

Patients with duodenal obstructions often have symptoms of nausea, vomiting, abdominal bloating and constipation.[5] This results in dehydration, electrolyte imbalance, malnutrition and general deterioration.[5,13] As a result of these complications, palliative chemotherapy becomes extremely challenging and won't necessarily be helpful in relieving symptoms.[14] Prompt relief of obstructions is required to palliate these symptoms and improve nutrition and quality of life.[7,10,15]

Palliative endoscopic duodenal stenting is a relatively less invasive procedure with acceptable efficacy has been reported.[10] It has been compared with palliative surgical intervention and provides relief of obstruction promptly. Gastrojejunostomy surgical bypass procedure is associated with a significant perioperative morbidity (up to 35%) and mortality (2%) and in a large group of patients (up to 31%) does not sufficiently relieve symptoms.[9,16] It is less expensive than gastrojejunostomy, surgical procedure performed for palliation with less hospital days.[17]

Previous studies have shown the complication rate of endoscopically placed duodenal stents is between 17% and 28%.[11] This is in keeping with our study, which showed a complication rate of 15%. Palliative duodenal stenting has been shown

Table 1: Demographics and clinical characteristics.

Total number of patients	61
Median age in years (range)	65 (40–96)
Gender, n (%) Male Female	 32 (52%) 29 (48%)
Ethnicity, n (%) NZ European NZ Māori Asian Pacific Islander Other European	 24 (40%) 13 (21%) 8 (13%) 11 (18%) 5 (8%)
Technical success	61/61 (100%)
Clinical success	60/61 (98%)
Primary diagnosis, n (%) Pancreatic adenocarcinoma Duodenal adenocarcinoma Gastric adenocarcinoma Others	 32 (52%) 13 (21%) 4 (7%) 12 (20%)

Figure 1: Primary diagnosis by category.

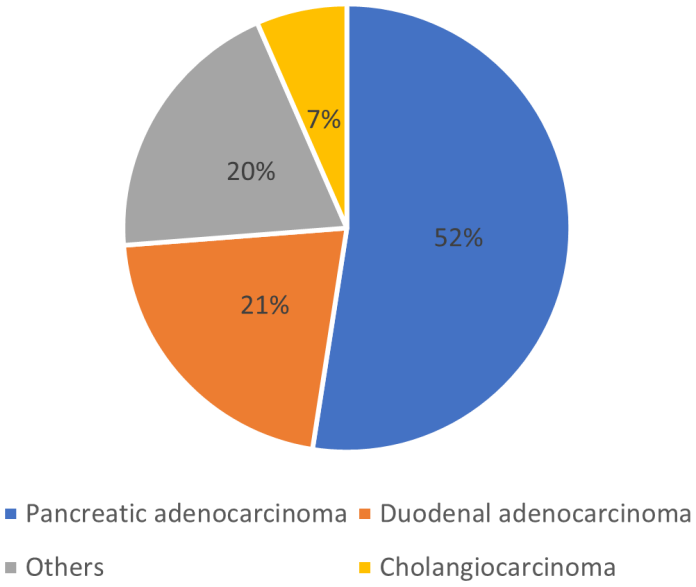

Figure 2: Type of stent used by category.

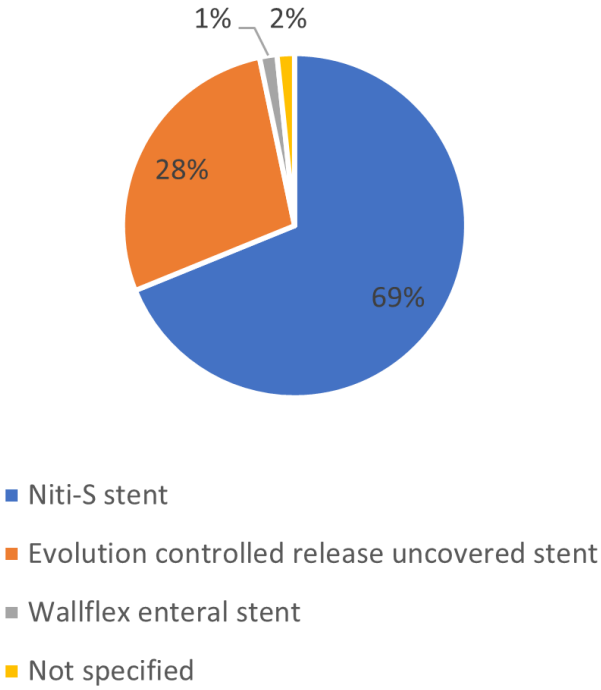

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Figure 3: Percentage of complications in each age group.

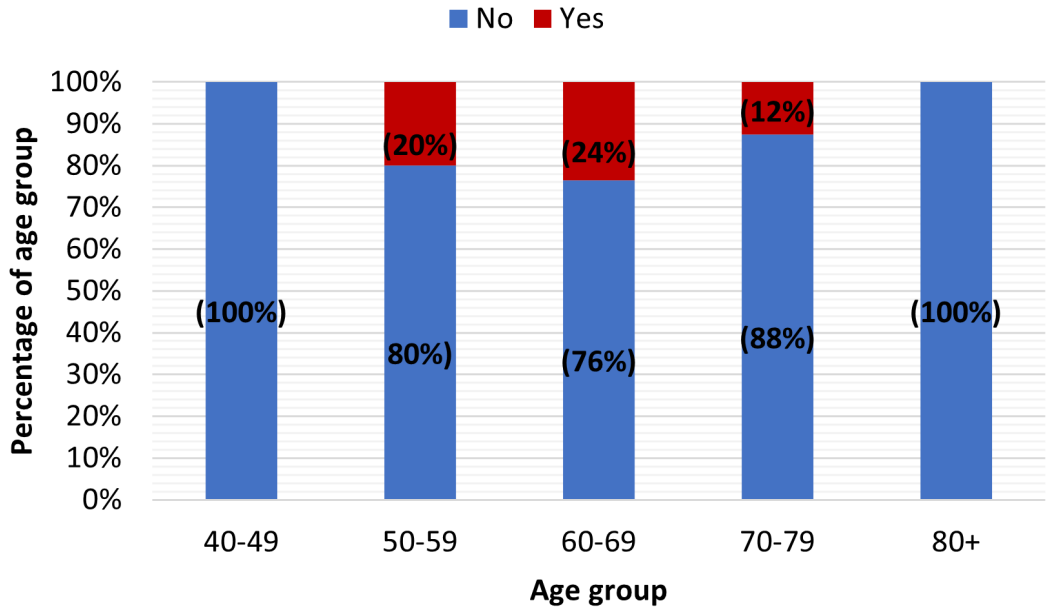

Figure 4: Percentage of complications in each ethnic group.

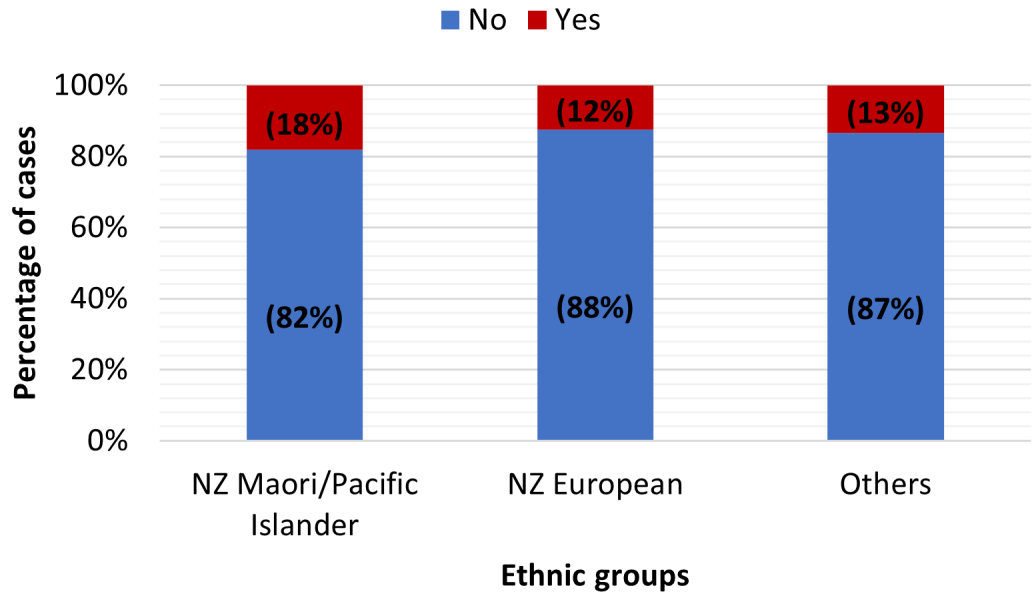

Figure 5: Percentage of complications with each involved stent type.

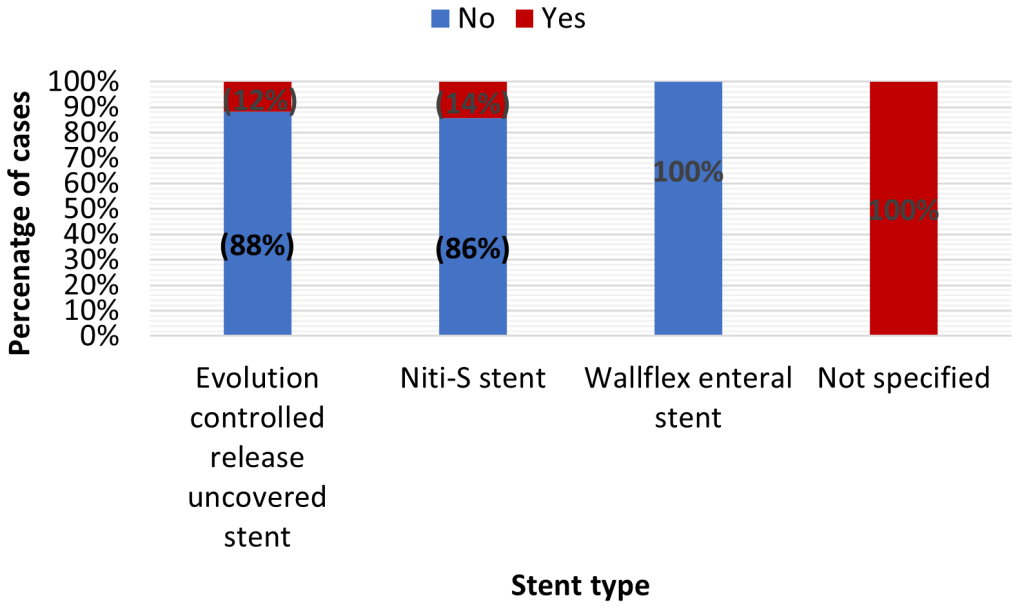

Figure 6: Number of complications in each category of primary diagnosis.

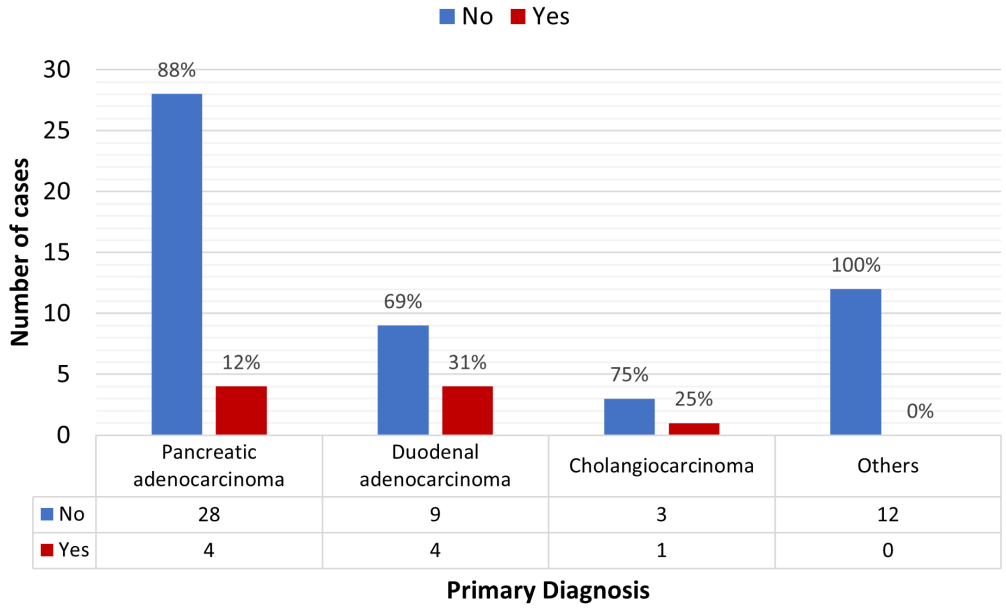

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Table 3: Counts and proportions of patient characteristics by complication.

Variables	No complication (N=52)	Complication (N=9)	Total	P-value*
Age				>0.95
<60	18 (85.7%)	3 (14.3%)	21	
>=60	34 (85%)	6 (15%)	40	
Gender				0.478
Female	25 (83.3%)	5 (16.7%)	30	
Male	27 (87.1%)	4 (12.9%)	31	
Ethnicity				0.98
Asian/other	7 (87.5%)	1 (12.5%)	8	
NZ Māori	10 (83.3%)	2 (16.7%)	12	
NZ European	21 (87.5%)	3 (12.5%)	24	
Pacific Islander	9 (81.8%)	2 (18.2%)	11	
Other European	5 (83.3%)	1 (16.7%)	6	
Primary diagnosis				0.127
Cholangiocarcinoma	3 (75%)	1 (25%)	4	
Duodenal adenocarcinoma	9 (69.2%)	4 (30.8%)	13	
Pancreatic adenocarcinoma	28 (87.5%)	4 (12.5%)	32	
Others	12 (100%)	0 (0%)	12	
Type of stent				0.357
Evolution controlled release uncovered stent	15 (88.2%)	2 (11.8%)	17	
Niti-S	36 (85.7%)	6 (14.3%)	42	
Wallflex enteral stent	1 (100%)	0 (0%)	1	
Not specified	0 (0%)	1 (100%)	1	

* Fisher exact test used.

to have a higher reintervention rate in comparison with surgery, due to complications such as stent obstruction and migration.[8,10] Stent patency is particularly influenced by malignant stent obstruction (via tumour growth) in about 15–20% of patients.[2,10,16] We observed a lower rate of malignant stent obstruction (8%) in comparison to previous studies, and in our study all but one patient were successfully treated with re-stenting. Rates of reintervention were 16% for a combination of stent migration and stent obstruction.

Uncovered stents are usually complicated by tumour ingrowth through the stent mesh. On the other hand, covered stents are complicated by stent migration despite lowering the risk of tumour ingrowth. Rates of reintervention to treat complications don't seem to differ significantly between the two types of stents.[8] Kim et al[11] showed that uncovered stents have a longer duration of stent patency and are more resistant to stent migration, making them preferable for patients with malignant duodenal obstruction.[10]

The higher complication rates identified in patients among the 60–69 age group, New Zealand Māori/Pacific Islander ethnic group, patients with the Niti- S stent and in those with duodenal adenocarcinoma as the primary diagnosis were not found to be statistically significant. This could be due to smaller numbers in our study. Larger studies are required to assess factors associated with complication rates.

Finally, no previous studies have commented on whether previous radiotherapy is a risk factor for bowel perforation in patients undergoing palliative duodenal stenting for malignant duodenal obstruction. However, it is considered a risk factor for perforation post stenting elsewhere in the upper GI tract.[12] In our study, seven patients in total had prior radiotherapy to chest or abdomen. Two of these patients subsequently developed a bowel perforation post duodenal stenting. Further studies are needed to assess whether prior radiotherapy is a risk factor for bowel perforation post duodenal stenting.

Conclusion

Duodenal stenting can be performed safely in most patients with malignant duodenal obstruction. Technical and clinical success is achieved in most patients and complication rates are low. Our results are similar to those in other published studies. This study could not adequately assess the factors associated with complications, due to smaller numbers. Larger studies are required to study this particular issue.

Competing interests:
Nil.

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Patch testing to plants: sensitisation associated with exposure to plants, essential oils and botanicals in cosmetics

Victoria L Murphy, Denesh C Patel, Steven R Lamb, Harriet S Cheng

ABSTRACT

BACKGROUND: Contact allergy to plants, particularly Compositae, presents with dermatitis and is diagnosed with skin patch testing. Sesquiterpene lactone mix is a common screening allergen for plant allergy. The rate of plant allergen sensitisation in New Zealand, which is affected by local horticultural factors, has not previously been documented.

AIMS: To investigate the rate of plant allergen sensitisation in New Zealand's regional population, characterise common allergens and reassess appropriate allergens for patch testing.

METHODS: Retrospective analysis of patient demographics and patch-test results over an eight-year period (2012 to 2020) was performed at a tertiary patch-test clinic in Auckland, New Zealand.

RESULTS: 820 patients completed patch testing. There was a 12.9% sensitivity rate (a positive reaction on patch testing) to at least one plant allergen and a 6.2% plant allergy rate (positive reaction of current relevance). The most frequent positive reactions were *Myroxylon pereirae* (n=38), colophonium (n=35) and sesquiterpene lactone mix (n=14). Of patients with a plant allergy (n=51), the allergy source was a botanical in a cosmetic product in 27 cases (52.9%), a plant in ten (19.6%) and an essential oil in two (3.9%).

CONCLUSIONS: Reactions to plant allergens were related to botanicals in cosmetics and creams, plants and essential oils. Rates of plant sensitisation in our cohort are comparable with international data.

Contact with plants may cause plant dermatitis (phytodermatitis) due to allergic, irritant and photosensitive (phytophotodermatitis) mechanisms.[1,2] Urticarial and airborne reactions to plant allergens can also occur. Allergic eczema (delayed-type hypersensitivity) due to plants is diagnosed with formal skin patch testing in dermatology clinics. Exposure to plants and subsequent development of allergy depends on local environmental and horticultural factors.

There are around 250 recognised contact sensitising families and over 10,000 species of contact sensitising plants worldwide, not counting poisonous plants. Compositae (daisy family) plants are significant culprits worldwide and include various weeds and edible and flowering plants. Patch testing with sesquiterpene lactone (SL) chemicals detects approximately 65% of Compositae allergy.[3] Some institutions utilise an additional Compositae mix (a 6% petroleum mix of chamomile, tansy, yarrow, Arnica and feverfew extracts), as well as related plant allergens including parthenolide and/or specific extracts prepared from individual plants in the Compositae family, depending on clinical suspicion.[4–6] Other plant sources for allergic eczema include diallyl disulfate (garlic), urushiol (poison ivy, Rhus tree and mango), primin (primula), colophonium (pine) and tuliposide A (tulips and alstroemeria).[7] Cross-sensitisation may arise between plant families; in particular, a third of Compositae-sensitised patients have allergy to fragrances, *Myroxylon pereirae* (Balsam of Peru), and colophonium (pine rosin), which are also of plant origin.[8]

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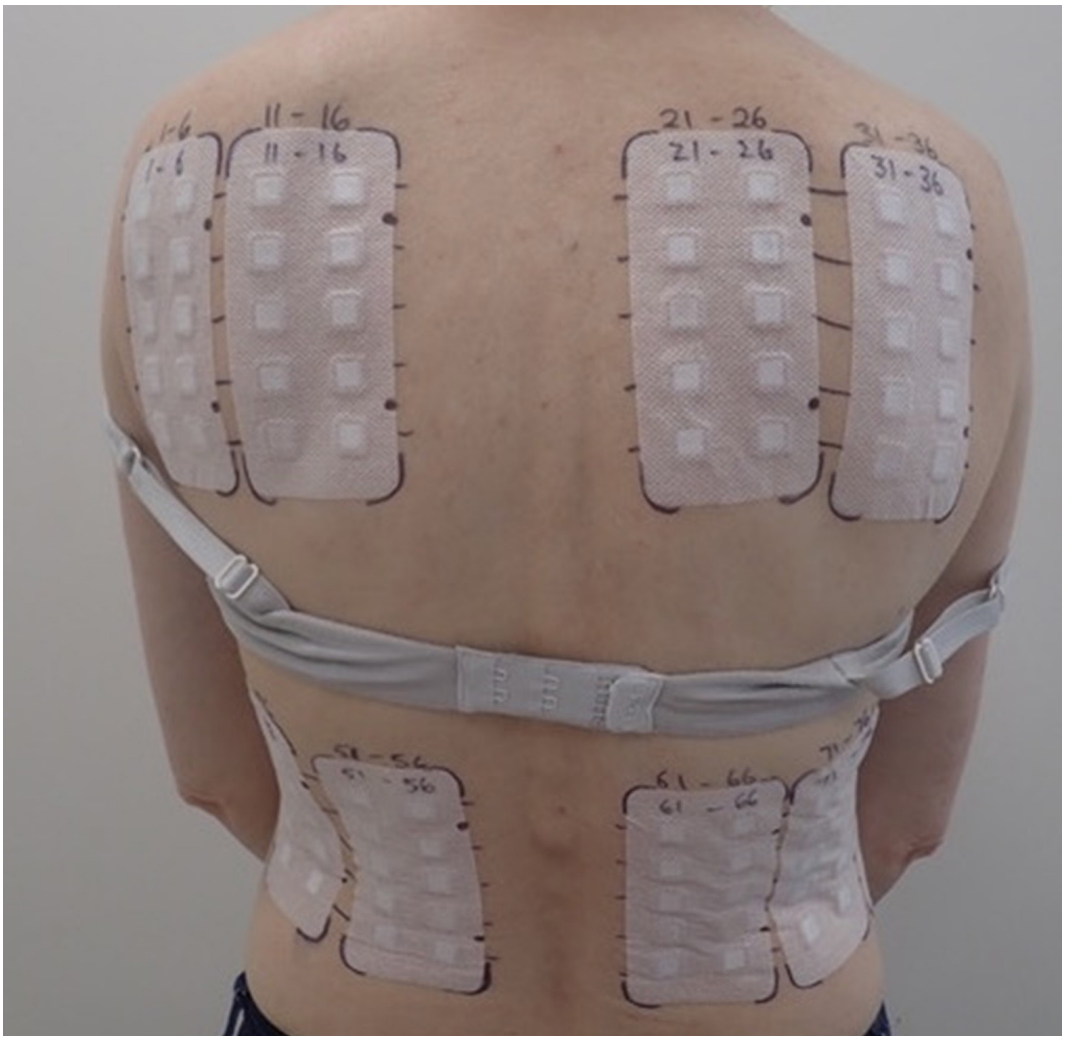
Allergic reactions to plants arise not only from contact with plants themselves, but also from cosmetic and personal-care products containing plant substances (often plant derived fragrances), essential oils and other products such as propolis drops.

Patch testing is a technique used to identify the cause of allergic contact dermatitis (delayed-type hypersensitivity) and verify the diagnosis (Figure 1) by controlled exposure to the suspected allergens in patients with a history and clinical picture of contact dermatitis. The most relevant and common allergens that cause contact dermatitis in the general population are recommended for use in most cases undergoing patch testing, as a 'baseline' or 'standard' series, with additional allergens added according to the clinical scenario.[9,10]

SL mix is included in the baseline series, which identifies many species of Compositae plants. The common cross-sensitising allergens colophonium and *Myroxylon pereirae* are also included in the baseline series. The plant series (17 allergens) is added if there is clinical suspicion of plant allergy. This series has not been updated recently: it is based on international plant allergens and may not contain optimised allergens for diagnosing plant allergies in New Zealand. Importantly, little is known about potential plant allergy related to rongoā and the traditional use of plants as topical botanical products in Māori medicine, which are not tested in our clinic (though patients' own products are tested where indicated). These allergens, including *Piper excelsum* (kawakawa), *Leptospermum*

Figure 1: Allergens applied to a patient's back during patch testing. Allergens stay in place for two days before removal.



scoparium (mānuka) and *Phormium tenax* (harakeke), are becoming increasingly used in botanical skin care products on the New Zealand market.

Reported data suggest that 5–10% of contact allergy in Europe is caused by plants and plant products, with the majority being occupational in nature.[1,11] International studies suggest a Compositae sensitisation rate in the patch-test population between 0.8% and 4.3%.[2–6] Examining patch-test data for our specific population is integral to detecting trends in rates of allergenicity. The aim of this study was to identify patients with plant allergy and determine the most common sensitising botanical allergens and exposures in a New Zealand population.

Methods

This study was a retrospective review of all patients patch tested at Auckland District Health Board (DHB) over an eight-year period. This is a tertiary service for patch testing and a central referral site for central Auckland (population 515,000) as well as the greater Auckland and Northland regions (populations 1,193,000 and 179,000, respectively).[12] Referrals are accepted from specialists only, predominantly dermatologists. Locality approval for this study was granted from Auckland Health Research Ethics Committee.

Individuals were routinely patch tested to the local baseline series (49 allergens) with additional series such as the plant and fragrance series and patient's own products added, as indicated by the clinical presentation.[13] Patch testing was performed with commercial allergens in plastic chambers on adhesive hypoallergenic tape (Chemotechnique, Vellinge, Sweden). Patches were removed on day two. Readings were recorded on day two and day five (2014 to 2017) or day seven (2018 to 2019).[14]

Population characteristics including gender, occupationally related dermatosis, presence of atopy, site of dermatosis, age and ethnicity were recorded in addition to the primary pre- and post-patch test diagnosis. The rates of positive and relevant positive patch-test reactions to plant allergens in the standard series, as well as the plant series and plant allergens in the fragrance series, were recorded (Appendix Table 1). Data was entered into a Microsoft Excel spreadsheet.

A positive reaction (+, ++ or +++) on the final reading was categorised as 'positive'. Irritant (IR) and doubtful positive (+/-) reactions were excluded. Reactions were graded in accordance with European Society of Contact Dermatitis guidelines. Relevance for positive reactions was recorded as current, past or unknown. Current relevance was defined as a positive patch test reaction to an allergen in contact with the skin in the distribution of the dermatosis.

Compositae allergy was defined as clinically diagnosed 'relevant positive' reactions to sesquiterpene lactone mix, and/or Compositae markers in the plant series (*Chamomilla romana*, *Arnica montana*, *Taraxacum officinale*, *Achillea millefolium*, *Chrysanthemum cinerariaefolium*, alpha-methylene-gamma-butyrolactone, *Tanacetum vulgare*, alantolactone, parthenolide, *Chamomilla recutita*).

Results

From July 2008 to December 2020, 859 individuals attended for patch testing, and 820 of these completed testing. Ethnicity analysis showed New Zealand European as the largest group (57.0%), followed by Asian (20.2%), Māori (7.9%) and Pacific peoples (6.3%). Compared to 2018 Census data, Asian patients are overrepresented while other groups, particularly Māori (16.5%), are underrepresented despite the incidence of eczema being higher in Māori.[15,16]

Overall, 54.9% of patients had at least one positive reaction (n=450). The most frequently positive allergens from the baseline series were nickel sulphate (metal, 23.0% sensitisation), fragrance mix I (6.8%), 4-phenylenediamine (hair dye, 6.0%), cobalt chloride (metal, 5.9%) and methylisothiazolinone/methylchloroisothiazolinone (preservative, 5.4%).

One hundred and six patients (12.9%) tested positive to at least one plant allergen (the 'plant-sensitised population'). In the sensitised population, almost half (n=51, 48.1%) of plant reactions were of current relevance (the 'allergic population') and the cause of allergic contact dermatitis. Thirty-four patients were tested to their own plant or botanical product, and positive

reactions were produced in five patients. There were no significant differences in patient age, gender, atopy or ethnicity between the overall patch-tested population and those with plant sensitisation (Table 1).

Sensitisation and relevance rates for plant allergens are summarised in Table 2. The most frequently positive plant allergens were *Myroxylon pereirae* (n=38, 4.6%), colophonium (n=35, 4.3%), SL mix (n=14, 1.7%), fragrance mix II (n=11, 1.3%), cinnamyl alcohol (n=5, 0.6%), hydroperoxides of linalool (n=5, 0.6%), parthenolide (n=5, 0.6%) and propolis (n=5, 0.6%).

In the allergic population (n=51), ten cases were sourced directly to plants, making the rate of plant allergy 1.2% (summarised in Table 3*)*. Eight of these cases were Compositae allergy and two were colophonium allergy, arising from contact with pine trees/resin. The remainder of relevant positive reactions were related to cosmetics and botanical creams (n=27), plant allergens in essential oils (n=2) and other sources (n=12). Two cases of plant allergy were occupational.

Discussion

Our rate of plant allergen sensitisation is in line with internationally reported rates, including Australia.[2–6] To our knowledge there is not prior New Zealand data for comparison. Geographically, sensitisation rates are expected to vary due to local horticultural factors, diverse patch-testing populations, including occupational exposures and different patch-test series and patch-testing methodologies.

We found plant reactions occurred most commonly with the baseline series allergens SL mix (marker for Compositae), colophonium and *Myroxylon pereirae*. SL mix represents the alpha-methylene-gamma-butyrolactones molecular family of allergens, while colophonium is from the terpene family, and *Myroxylon pereirae*, which is primarily from the terpene family, contains a mixture of components including cinnamic acid, benzoic acid and eugenol. *Myroxylon pereirae* (Balsam of Peru) is most commonly found as a vanilla/cinnamon fragrance in perfumes, deodorants and cosmetics, as well being an ingredient in a popular pawpaw lip balm. Colophonium (pine resin) is also found most commonly in cosmetics such as mascara, as well as in sticking plaster adhesive. SL mix is a component in plants of the Compositae family, which includes species of flowers including daisy, aster and sunflower. The main source of allergy to this allergen is through exposure to the plant flower or pollen, though Compositae

Table 1: Clinical characteristics of patients patch tested at Auckland City Hospital between 2008 and 2020 (n=820).

Characteristic	Overall patch-tested population n=820 (%)	Plant-sensitised population n=106 (%)	P-value
Female	557 (67.9)	76 (71.7)	0.430
Occupational cause for dermatosis	59 (7.2)	9 (8.5)	0.631
Atopy	501 (61.1)	71 (67.0)	0.242
Site of dermatosis			
Hands	233 (28.4)	39 (36.8)	0.075
Face	194 (23.7)	25 (23.6)	0.984
Legs	14 (1.7)	0 (0.0)	0.173
Age > 40 years†	471 (57.4)	61 (57.5)	0.984
Positivity rate (≥1 positive reaction)	450 (54.9)	-	-

†Mean age = 45 (standard deviation 17.1).

Table 2: Reactions to plant allergens in patients patch tested at Auckland City Hospital between 2008 and 2020 (n=820).

Plant allergen tested	Positive	Relevant positive	Sensitisation rate in overall patch-tested population (n=820)	Relevant/ positive %	Patients tested
Myroxylon pereirae	38	20	4.6%	52.6%	820
Colophonium	35	14	4.3%	40.0%	820
Sesquiterpene lactone mix	14	6	1.7%	42.9%	820
Fragrance mix II	11	4	1.3%	36.4%	820
Cinnamyl alcohol	5	3	0.6%	60.0%	34
Hydroperoxide of linalool	5	4	0.6%	80.0%	35
Parthenolide	5	2	0.6%	40.0%	11
Propolis	5	3	0.6%	60.0%	92
Cinnamal	3	3	0.4%	100.0%	108
Isoeugenol	3	2	0.4%	66.7%	108
Oakmoss absolute	3	3	0.4%	100.0%	108
Ylang-ylang oil	3	1	0.4%	33.3%	108
Citral	3	0	0.4%	0.0%	108
Tanacetum vulgare (tansy)	3	2	0.4%	66.7%	70
Lichen acid mix	3	0	0.4%	0.0%	70
Eugenol	2	2	0.2%	100.0%	108
Hydroxycitronellal	2	1	0.2%	50.0%	108
Lavender absolute	2	2	0.2%	100.0%	108
Cananga oil	2	2	0.2%	100.0%	108
Hydroperoxide of limonene	2	1	0.2%	50.0%	11
Amyl cinnamyl	1	0	0.1%	0.0%	108
Geraniol	1	0	0.1%	0.0%	108
Vanillin	1	1	0.1%	100.0%	108
Rose oil absolute	1	1	0.1%	100.0%	108
Geranium oil bourbon	1	1	0.1%	100.0%	108
Sandalwood oil (Indian)	1	1	0.1%	100.0%	108
Farnesol	1	1	0.1%	100.0%	108
Citronellol	1	1	0.1%	100.0%	108

Table 2: Reactions to plant allergens in patients patch tested at Auckland City Hospital between 2008 and 2020 (n=820) (continued).

Plant allergen tested	Positive	Relevant positive	Sensitisation rate in overall patch-tested population (n=820)	Relevant/ positive %	Patients tested
Hexyl cinnamic aldehyde	1	1	0.1%	100.0%	108
Coumarin	1	0	0.1%	0.0%	108
Diallyl disulphide (garlic)	1	0	0.1%	0.0%	70
Achillea millefolium (yarrow)	1	1	0.1%	100.0%	70
Chrysanthemum cinerariaefolium (Chrysanthemum)	1	1	0.1%	100.0%	70
Narcissus poeticus	0	0	0.0%	0.0%	108
Jasmine absolute, Egyptian	0	0	0.0%	0.0%	108
Chamomilla romana (Roman chamomile)	0	0	0.0%	0.0%	70
Arnica montana (mountain tobacco)	0	0	0.0%	0.0%	70
Taraxacum officinale (dandelion)	0	0	0.0%	0.0%	70
Alpha-methylene-gamma-butyrolactone	0	0	0.0%	0.0%	70
Alantolactone	0	0	0.0%	0.0%	70
Chamomilla recutita (German chamomile)	0	0	0.0%	0.0%	70
Usnic acid	0	0	0.0%	0.0%	70
Atronorin	0	0	0.0%	0.0%	70
Evernic acid	0	0	0.0%	0.0%	70
Total	162	84	-	-	-

Table 3: Summary of patients with diagnosed contact allergy to plants.

Case	Age at testing	Gender	Ethnicity	Atopy	Occupational	Clinical diagnosis and Localisation	Source of allergy	Plant allergy type	Positive plant marker reactions	Positive own plant product reactions	Other positive reactions
1	62	Female	NZ European	Yes	No	Atopic dermatitis + allergic contact dermatitis (hands)	Gardening with Compositae plants	Compositae allergy	SL mix	No	Cobalt, nickel
2	48	Female	NZ European	Yes	No	Allergic contact dermatitis + atopic dermatitis (generalised)	Gardening with Compositae plants	Compositae allergy	SL mix, tansy, lichen acid, parthenolide	No	Cobalt, nickel, own Revlon Crème Make-up
3	30	Female	Not stated	Yes	Yes (Zoo keeper)	Allergic contact dermatitis (hands and face)	Zoo worker—occupational contact with Compositae plants	Compositae allergy	SL mix, parthenolide	Not tested	Thiuram
4	31	Female	Māori	Yes	No	Allergic contact dermatitis (generalised)	Airborne contact dermatitis to Compositae plants	Compositae allergy	Colophonium, SL mix, abeitic acid, SL mix 0.1%	No	-
5	44	Male	NZ European	Yes	No	Allergic contact dermatitis (hands)	Incidental exposure to Compositae plants	Compositae allergy	Yarrow, *Chrysanthemum cinerariaefolium*, tansy	Not tested	-
6	71	Male	NZ European	No	No	Pompholyx + allergic contact dermatitis (hands)	Gardening, plant types not identified	Compositae allergy	SL mix, parthenolide	Not tested	-

Table 3: Summary of patients with diagnosed contact allergy to plants (continued).

Case	Age at testing	Gender	Ethnicity	Atopy	Occupational	Clinical diagnosis and Localisation	Source of allergy	Plant allergy type	Positive plant marker reactions	Positive own plant product reactions	Other positive reactions
7	53	Male	Not stated	No	Yes (Shop keeper)	Allergic contact dermatitis (hands)	Greengrocer—occupational contact with plants	Compositae allergy	SL mix, tansy	Not tested	-
8	73	Male	NZ European	No	No	Psoriasis + allergic contact dermatitis (palmoplantar)	Gardening with Compositae plants	Compositae allergy	SL mix, parthenolide	Not tested	Lidocaine hydrochloride
9	60	Female	Korean	No	No	Allergic contact dermatitis (face)	Contact with pine tree resin	Colophonium (pine) allergy	Colophonium, *Myroxylon pereirae*, propolis, abeitic acid	No	Neomycin, nickel, tixocortol-1-pivalate
10	9	Female	NZ European	No	No	Allergic contact dermatitis (hands)	Contact with Christmas tree	Colophonium (pine) allergy	Colophonium	Not tested	-

extracts may also be used in cosmetics (eg, calendula oil).

Botanical cosmetics and topical botanical products were the most common exposures responsible for allergy overall, rather than the plants themselves. The most common medical or cosmetic motivation for using topical botanical products was as moisturiser (face and body creams), such as to manage eczema. A Belgian study had a lower sensitisation rate of 0.8% to topical herbal medicines, though definitions of topical botanical products may vary between studies.[6] The Belgian study also showed that many patients did not react to the commercial allergens in the patch series, but only to the products used. This suggests testing of patients' own cosmetic and other topical products is vital, particularly considering that botanical allergens not available in our botanical series, including those related to rongoā Māori medicine, are increasingly being used in topical skin care products on the New Zealand market.[17,18]

The plant series used in our centre are based on international data on sensitisation. Plants common in the northern hemisphere may be less relevant for New Zealand, and testing patients' own plant products is paramount to discover unsuspected allergens.[6] Although there is little data on the epidemiology of plant allergy in New Zealand, in a 2001 publication Grieg and Rademaker observed that in their clinical experience most New Zealand allergic reactions are due to exotic species, such as tulips, daffodils and grevillea.[19] *Primula obconica*, introduced to New Zealand in 1993, has caused a number of allergic reactions, and *Toxicodendron succedaneum* (Rhus tree) is a significant problem in the North Island, having caused 20 cases of phytodermatitis at Grieg and Rademaker's centre in 1993. New Zealand case reports on phytodermatitis include *Lavandula angustifolia* (lavender), *Ficus carica* (fig tree), *Grevillea robusta* (grevillea), *Toxicodendron succedaneum* (Rhus tree), *Heracleum mantegazzianum* (hogsbane), *Hydrangea macrophylla* (hydrangea), *Actinidia chinensis* (kiwifruit vine), *Toxicodendron radicans* (poison ivy and poison oak) and *Asparagus officinalis* (asparagus).[20–27] Data suggest that cross-sensitisation from SL mix may pick up sensitivity to relevant plants in New Zealand. However, our patch-test data are still limited in the testing of New Zealand native plants.

Little clinical data are available about potential plant allergy related to rongoā (traditional Māori medicinal practices), and Māori patients who may be more likely to have these exposures are underrepresented in our patch testing population. Plants such as *Piper excelsum* (kawakawa), *Phormium tenax* (harakeke), *Pseudowintera colorata* (horopito), *Pomaderris kumeraho* (kūmarahou) and Leptospermum scoparium (mānuka) are culturally significant and traditionally used in rongoā, and now they are more commonly incorporated into proprietary products such as eczema creams and moisturisers.[28] Although these plants are not included in our plant-testing series, there may be some cross-reactivity with existing plant markers: for example, mānuka oil, horopito and kawakawa contain terpene derivatives that may cross react with colophonium and *Myroxylon pereirae*.[28,29] We found just one case of allergic contact dermatitis to a native New Zealand plant in the literature, with a woman reacting to *Pseudowintera colorata* (horopito).[30] The leaves of horopito are used in rongoā to treat fungal skin infections, venereal diseases, stomach pain and diarrhoea.[31]

In addition to New Zealand native plants, *Melaleuca alternifolia* (tea tree oil) may be of particular relevance in Australasia. Allergy to *Melaleuca alternifolia* has been identified at much higher rates in Australia (3%) compared to North American and European groups, where prevalence is reported at 0.1–0.15%. Older Australian studies have found rates of up to 3–5% and this has led to inclusion of melaleuca oil in the Australian Baseline Series.[10] This Australian plant-derived essential oil from the family Myrtaceae is frequently used in herbal and traditional medicines of Australia and New Zealand and may also be relevant to our population. We found five cases of *Melaleuca alternifolia* sensitisation in our population with exposures including cosmetics and essential oils.

In a 2018 Danish study, SL was among the top seven allergens associated with polysensitisation (sensitisation to multiple allergens on patch testing).[8] Meta-analysis of contact allergy in 28 studies from 2007 to 2017 in

Europe and North America also reported that there is significant cross-reactivity between Compositae mix and fragrance mix, *Myroxylon pereirae* and colophonium.[32] Our centre shows similar polysensitisation rates: 72.7% of the plant allergy cases reacted to more than one plant allergen, and 54.5% reacted to more than two plant allergens.

A Singaporean study conducted on ten patients with contact dermatitis to topical traditional Chinese herbal medicine found three cases of allergic contact dermatitis with reactions to *Myroxylon perierae* and fragrance mix I.[33] Chinese herbal plant extracts notably contain terpenes (eg, camphor and menthol) known to cross-react with colophonium (terpene family) and *Myroxylon pereirae* (terpene family), as well as essential oils (eg, eucalyptus and cinnamon), suggesting cross-reaction to plant allergens in our baseline series may pick up allergy to plant allergens in traditional medicine. Asian patients were also over-represented in our cohort. This may be related to high eczema rates in Asians, a yet uncharacterised susceptibility to contact allergy or cultural factors, including use of plants in Chinese traditional medicines.[34]

Our study has a number of limitations. Firstly, in some cases the retrospective design with data collected from clinical notes led to difficulty interpreting the relevance of plant reactions. Often the specific plant species of exposure was unknown or not documented. Additionally, patients are only patch tested to additional allergen series where there is clinical suspicion of allergy, and for practical reasons the full plant series is not tested sequentially. Untested allergens are assumed to be negative, but this may result in a falsely low sensitisation rate. Due to limitations in clinic staffing, the final reading changed from day five to day seven in 2018. The ideal timing for final patch test readings is day three or four and day seven.[14] The late reading at our centre may lower sensitisation rates.

In summary, we report a sensitisation rate of 12.9% to plant allergens in a New Zealand tertiary referral population. The most frequent reactions were to terpenes (*Myroxylon pereirae* and colophonium), with the most frequent exposures to these being botanical ingredients in cosmetics and personal care products. Of those with true plant allergy, Compositae plants were the most frequent culprits, followed by pine. Further research is needed into the potential for irritant reactions and sensitisation to New Zealand native plants, particularly those of cultural importance in traditional Māori medicine.

Appendix

Appendix Table 1: Plant allergens used in sequential and additional testing at Auckland City Hospital.

Series	Allergen name	Concentration and vehicle
Baseline	Colophonium	20.0% pet
	Myroxylon pereirae	25.0% pet
	Sesquiterpene lactone mix	0.1% pet
	Propolis	10.0% pet
Fragrance	Cinnamal	1.0% pet
	Cinnamyl alcohol	2.0% pet
	Amyl cinnamyl	2.0% pet
	Eugenol	2.0% pet
	Isoeugenol	2.0% pet
	Geraniol	2.0% pet
	Oakmoss absolute	2.0% pet
	Hydroxycitronellal	2.0% pet
	Narcissus poeticus	2.0% pet
	Vanillin	10.0% pet
	Lavender absolute	2.0% pet
	Cananga oil	2.0% pet
	Rose oil absolute	2.0% pet
	Ylang-ylang oil	2.0% pet
	Geranium oil bourbon	2.0% pet
	Jasmine absolute, Egyptian	2.0% pet
	Sandalwood oil, Indian	2.0% pet
	Citral	2.0% pet
	Farnesol	5.0% pet
	Citronellol	1.0% pet
	Hexyl cinnamic aldehyde	10.0% pet
	Coumarin	5.0% pet
	Fragrance mix II	14.0% pet
	Hydroperoxide of limonene	0.3% pet
	Hydroperoxide of linalool	1.0% pet

Appendix Table 1: Plant allergens used in sequential and additional testing at Auckland City Hospital.

Series	Allergen name	Concentration and vehicle
Plant	*Chamomilla romana*	1.0% pet
	Diallyl disulphide	1.0% pet
	Arnica montana	0,5% pet
	Taraxacum officinale	2.5% pet
	Achillea millefolium	1.0% pet
	Propolis	10.0% pet
	Chrysanthemum cinerariaefolium	1.0% pet
	Sesquiterpene lactone mix	0.1% pet
	Alpha-methylene-gamma-butyrolactone	0.01% pet
	Tanacetum vulgare	1.0% pet
	Alantolactone	0.033% pet
	Lichen acid mix	0.3% pet
	Parthenolide	0.1% pet
	Chamomilla recutita	1.0% pet
	Usnic acid	0.1% pet
	Atronorin	0.1% pet
	Evernic acid	0.1% pet

Competing interests:
Nil.
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Ciguatera poisoning and confirmation of ciguatoxins in fish imported into New Zealand

J. Sam Murray, D. Tim Harwood, Lesley Rhodes

ABSTRACT

Ciguatera poisoning has caused illnesses in New Zealand through the consumption of contaminated reef fish imported from Pacific Islands. In May 2020 five people became ill and one was hospitalised following the consumption of Fiji Kawakawa (camouflage grouper; *Epinephelus polyphekadion*). The fish was purchased in New Zealand but imported from Fiji. The meal remnants were analysed for ciguatoxins, the causative compounds of ciguatera poisoning, and showed the presence of the three main toxic fish metabolites. Other fish tested from the same shipment did not contain detectable levels of ciguatoxins, indicating they were likely not toxic.

Ciguatera poisoning (CP) is the most common non-microbial food-borne illness in the world. It is prevalent in the circumtropical regions of the world and is caused by the consumption of fish, invertebrates, gastropods and bivalve molluscs contaminated with ciguatoxins (CTXs) and possibly maitotoxins (MTXs).[1,2]

Although fatalities are uncommon, there is no reliable treatment or antidote, and therefore cases of chronic illness provide most of the data for epidemiological assessments.[3] Folk remedies based on the local flora are used in many Pacific Islands, and intravenous mannitol has been suggested as a possible treatment,[4] although the efficacy of mannitol has been disputed.[5] Due to the lack of a proven antidote, treatment is largely supportive and symptom-driven, which complicates the diagnostic process.

All CP cases reported in New Zealand to date have resulted from the consumption of contaminated reef fish by Pacific Island tourists who have returned to New Zealand from the Pacific Islands and become ill, or from the consumption of reef fish imported into New Zealand. Several cases of CP, linked to moray eel (Muraenidae sp.) brought back from Samoa, were reported in Wellington, New Zealand, in 2016.[6] Several more CP cases were diagnosed in 2019 on the basis of symptoms following the consumption of moray eel brought back from the Kingdom of Tonga and home-smoked.[7] No cases of CP from locally caught and consumed fish have been reported in New Zealand.

Case report

From 10 March until 21 May 2020, Fiji Kawakawa (camouflage grouper; *Epinephelus polyphekadion*) imported from Fiji was sold by Krazy Mart in Christchurch, New Zealand. At the beginning of May 2020, five adults from two families became ill after consuming some of the imported fish. Two were females aged in their forties and fifties and three were males aged between 19 and 58 years old. The eldest male, who had consumed four times the amount of the other diners, was hospitalised within 48 hours of consuming the fish meal. The symptoms were typical of CP (inversion of hot and cold, paraesthesia and dysaesthesia) and the patients were clinically diagnosed as suffering from CP.

Methods

Meal remnants from the intoxication event (fried fish and fried fish curry; Figure 1) were received at Cawthron Institute on 2 June

2020. The samples had the skin and bones removed prior to being homogenised in their entirety. Analysis was performed using an in-house liquid chromatography-tandem mass spectrometry (LC-MS/MS) quantitative method for accurate and specific detection of selected CTXs and MTXs.[8] The most commonly implicated CTX fish metabolite in the Pacific region, P-CTX-1B, had a limit of quantitation (LoQ) of 0.1 µg/kg.

Fish imported in the same batch as those that caused the intoxication event were recalled and tested using the LC-MS/MS method above. They were all labelled 'Fiji Kawakawa' but were in fact a mix of camouflage grouper (*Epinephelus polyphekadion*) and another, somewhat-morphologically-similar species, squaretail grouper (*Plectropomus areolatus*).

Results

Results of the analyses, as reported to the Canterbury District Health Board, had quantifiable levels of P-CTX-1B. The fried fish sample contained 0.29 µg/kg and the curried fish sample contained 0.21 µg/kg P-CTX-1B. The curried fish sample contained less fish, although it had a coconut base. As CTXs are lipophilic, the whole sample was tested. Two additional CTX fish metabolites, 52-*epi*-54-deoxyCTX-1B (P-CTX-2) and 54-deoxyCTX-1B (P-CTX-3), were also easily detected in both samples. However, as calibrated reference material was not available, they were not able to be quantified.

Associated fish from the same shipment as the recalled product were also tested but were negative for the fish metabolite CTXs.

Discussion

Pharmacological assessments have shown that CTXs bind to site five of the voltage-gated sodium channel found in muscles. This binding causes the activation of the sodium/potassium ion pump by modifying the voltage-dependence across the membrane and thereby creating an influx of sodium ions into the cell.[9,10] Intoxication manifests as a wide array of symptoms, including gastrointestinal discomfort (eg, vomiting, diarrhoea, nausea), neurological impairment (eg, inversion of hot and cold, dysaesthesia, paraethesia) and/or cardiovascular complications (eg, hypotension, bradycardia).[11,12] Interestingly, differences in symptoms and intrinsic potencies can be geographically assigned (eg, the Caribbean and the Pacific), which helps with clinical diagnosis.[10,11] This is most likely due to structure-activity and pharmacokinetic differences between the different CTX analogues. The onset of clinical symptoms can appear from 2–30 hours after consumption of ciguatoxic fish, and three key neurological symptoms are characteristic of CP from the Pacific region: inversion of hot and cold, dysaesthesia and paraesthesia.[12,13]

The toxins found in fish that cause the poisoning syndrome have their origins in a single-celled microalgae from the genus *Gambierdiscus* (Dinophyceae). *Gambierdiscus* is epiphytic on macroalgae, eel grasses and coralline turfs and is consumed with the host substrate by herbivorous and coral-grazing reef fish. Omnivorous and carnivorous fish prey on these species and the toxins are biotransformed and biomag-

Figure 1: Remnants of fish meals linked to ciguatera poisoning cases in Christchurch, New Zealand.

nified up the marine food web.[14] The only known CTX producer in New Zealand waters is *Gambierdiscus polynesiensis*, which has been isolated from Rangitāhua (the Kermadec Islands), a New Zealand territory approximately 1,000 km northeast of the mainland.[15] The species has also been isolated throughout the tropical South West Pacific. A related genus, *Fukuyoa* (previously classified as *Gambierdiscus*), has been isolated from the Bay of Islands, but does not produce CTXs or MTXs.[15]

In the Pacific region, P-CTX-1B has been well documented in many fish species[16] and is typically the dominant CTX analogue in ciguatoxic fish. No regulatory limits have been officially set for CTXs, although the United States Food and Drug Administration has established a guidance level of 0.01 µg/kg P-CTX-1B equivalents for Pacific CTXs and 0.1 µg/kg C-CTX-1 equivalents for Caribbean CTXs.[17] The difference between the two levels is due to the differences observed in the potency between these CTX analogues. The meal remnants linked to this poisoning had 0.29 and 0.21 µg/kg P-CTX-1B for the fried fish and fish curry, respectively, which is well above the guidance level. Although analytical methods are essential for regulatory monitoring, globally there is currently no method that can accurately and specifically quantify the different CTX analogues down to this level.

The intoxication event presented here is from fish imported from Fiji and sold in New Zealand. It is important to also focus on the increasing sea surface temperatures and changes in the prevailing currents due to climate change. This is causing an expansion of the sub-tropical/temperate latitudes, which in turn means the habitable range of *Gambierdiscus* is also expanding. This is evident as CP in Australia has historically been along the coast of Queensland, however in recent years fish caught in New South Wales waters have caused CP events.[18] The coastal waters around New Zealand are also warming up and therefore the risk of locally contracted cases of CP is increasing.[15,19]

Conclusions

The illnesses reported in Christchurch in May 2020 and diagnosed as CP were caused by fish that had been imported from Fiji and which were shown to be contaminated with CTXs. The risk of suffering from CP after eating reef fish from the Pacific region is real and should be considered in any instance where there is illness following consumption of such a meal. Testing of meal remnants will help confirm a CP diagnosis, but only the fish eaten is of interest, as CTX concentrations differ widely between individual fish, even from the same catch.

Competing interests:
Nil.
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Evaluating barriers to access for cataract surgery in Waikato: analysis of calculated driving distance and visual acuity

Ben Wilkinson, James McKelvie

ABSTRACT

AIM: An important determinant of health is access to healthcare, which is influenced by geographic location. This cross-sectional study aimed to investigate whether presenting visual acuity or patient demographic variables, including ethnicity, were associated with geographic proximity to primary and secondary ophthalmic services.

METHODS: Demographics for all patients referred within the Waikato District between October 2017 and March 2019 that met the threshold for publicly funded cataract surgery were analysed. GPS coordinates for all patient and optometrist addresses were obtained from referral data using RStudio, the OpenStreetMap and Google Maps Application Programming Interfaces. The driving distance and driving time for each patient to travel to their referring optometrist were calculated. Quality-of-life data were obtained from the Impact on Life questionnaire completed at time of referral. Analysis of visual acuity, driving distance, age, ethnicity and gender was completed using univariate and multivariate regression. Furthermore, a comparative analysis of Māori and New Zealand European defined as having remote access (driving distance of >5km from optometrist) was completed.

RESULTS: A total of 1,260 patients were included for analysis. Multivariate analysis showed no significant association between driving distance and visual acuity. Comparative analysis of Māori (n=94) and New Zealand European (n=468) defined as having remote access (driving distance of >5km from optometrist) showed Māori had significantly worse visual acuity than New Zealand Europeans (LogMAR 0.874 vs 0.577) at the time of referral. No significant difference was found in quality of life. Māori were on average younger than New Zealand European (67.3 vs 76.9 years of age). Driving time and distance were on average 27% longer for Māori compared with New Zealand Europeans defined as having remote access (37.8 vs 29.0km, 34.1 vs 27.6 minutes).

CONCLUSIONS: Māori presenting with cataract typically are younger and have lower visual acuity than New Zealand European. Longer driving distances represent a potential geographic barrier for Māori to access ophthalmic care and referral to tertiary services within the Waikato District. No significant association was found between driving distance and visual acuity.

The World Health Organization (WHO) suggests that equitable access to quality healthcare is an essential goal of any health system.[1] Accurate description of the concept of 'accessibility' has proven difficult given the multitude of involved factors.[2,3] WHO suggests accessibility encompasses four dimensions: non-discrimination, physical accessibility, economical accessibility and information accessibility.[1]

In New Zealand, rural residency is associated with decreased access to healthcare, ethnic health disparities and inequity in access to ophthalmic healthcare.[4] The scale of this issue may be underreported due to inaccuracies within Stats NZ's definition of rural/urban healthcare access data.[5] For example, calculations suggest that over 43% (340,000/779,620) of people who use rural health services were incorrectly classified as

urban in 2006 census data. Accurately quantifying geographic barriers to healthcare is important for reducing social inequality and ethnic health disparities within New Zealand.[6–10]

Geographic information systems can be used to calculate patient (domicile) proximity to healthcare.[11–14] Driving time, in particular, has been used to estimate to the accessibility of medical care in ophthalmology, cardiology and emergency medicine.[13,14] Previous reports have confirmed that a longer travel time is associated with a reduced utilisation of general practitioners (GP).[15–17] Within New Zealand, research to quantify physical access to healthcare is limited.[9,15,18] Barriers to accessing healthcare in New Zealand vary according to region.[19] The relative importance of geographic location in accessing ophthalmic care in New Zealand has not been previously reported. To our knowledge, this is the first study in New Zealand to evaluate the physical accessibility of ophthalmic care by directly calculating driving routes and driving times. The hypothesis for the current study is that decreased geographic proximity to the referring optometrist would correlate with worse visual acuity at the time of referral for cataract surgery. This study investigates the roles of geographic proximity, ethnicity and patient demographics in determining access to ophthalmic care within the Waikato District in New Zealand.

Methods

This study met the criteria for exemption from ethics formal approval on the basis of the observational and non-interventional design.[20] Street addresses of the 12 optometry practice addresses within the Waikato District were obtained from the New Zealand Ministry of Health 2019 facility code tables and tabulated using Microsoft Excel. Referral data from 1,264 patients in the Waikato District that met the threshold for publicly funded cataract surgery between October 2017 and March 2019 was obtained via CatTrax online referral system. The CPAC threshold in Waikato during the study period fluctuated from 56 to 62. All community referrals for cataract surgery in Waikato are made via CatTrax by optometrists, and all fields of the online form must be completed to submit a referral. Visual acuity at time of referral, patient home address, impact of visual impairment on quality of life, optometrist attended and patient-reported ethnicity were extracted from referral data for analysis. Self-reported ethnicity was recorded with CatTrax using the standard census ethnicity question. For analysis we used prioritised output, whereby each respondent was allocated to a single ethnic group using the Health Informations Standards Organisation Ethnicity Data Protocols prioritisation tables at level 2 classification. Visual acuity in the worse seeing eye, as well as best binocular visual acuity, was converted from Snellen into LogMAR form and treated as a continuous variable. The impact of visual impairment on the patient's quality of life was assessed via the Impact on Life questionnaire, which is included in all referrals. The questionnaire comprises six questions that each assess the impact of visual impairment on an aspect of the patient's life (social Interaction, personal Interaction, ability to fulfill responsibilities to others, personal care, personal safety and leisure activities). Location data were converted to global positioning satellite (GPS) coordinates by geocoding the addresses using RStudio and the Open Street Mapping (OSM) Application Programming Interface (API).

Optometrists are located within all major towns and cities in the Waikato District. Driving time and distance for a patient to commute to their selected referring optometrist was calculated for each patient using the Open Source Routing Machine (OSRM). OSRM calculates the shortest route, defined as the path of shortest driving time from one location to another. OSRM utilises the geometries for every drivable surface (road, streets and highways), along with the speed limit for each segment of the road. Access via public transport services were not calculated.

Univariate analysis of driving time and visual acuity (binocular visual acuity and worse-seeing eye LogMAR) was completed. Four patients were excluded from analysis as their addresses were outside of Waikato DHB catchment. Subsequent multivariate regression analysis of all data, incorporating ethnicity, age and gender, was performed. Furthermore, Students t-test was used to

perform a comparative analysis of Māori and New Zealand European patients defined as having 'remote access' (>5km driving distance from home address to optometrist). Threshold distances of 4km and 5km to primary care have been used in reporting 'poor access' and 'remote access', respectively.[21,22] We consider optometry to be primary care.Therefore we defined 5km as the threshold distance for remote access and excluded those living <5km driving distance to referrer from this aspect of our analysis. Ninety-four Māori patients and 468 New Zealand European patients were included in this analysis. Other ethnicities were excluded given the small number of participants in these groups. Data analysis was completed using RStudio (available at: http://r-project.org).

Results

Driving routes and times to the nearest optometrist and actual optometrist attended were mapped for a total of 1,260 patients within the Waikato District. A total of 12 optometry practices were geo-coded from New Zealand Ministry of Health 2019 facility code tables and referral data. OpenStreetMap and Google Maps were used to calculate the shortest driving time and distance to the nearest optometrist (Figure 1).

Visual acuity at referral was obtained, as well as demographic factors including ethnicity, age and domicile street address (Table 1). Multivariate analysis showed no statistically significant correlation between driving distance and visual acuity when controlling for ethnicity, age and gender (p-value=0.60).

Statistically significant differences were found on comparative analysis of Māori and New Zealand European patients defined as having remote access. Driving distance to the referring optometrist averaged 27% longer for Māori compared with New Zealand Europeans with remote access (37.8 vs 29.0km, p-value=0.006) (Figure 2). The mean age at referral varied, with Māori presenting at a younger age than New Zealand European with remote access (67.3 vs 76.9, p<0.001). Patients of Māori ethnicity were referred with significantly worse visual acuity than New Zealand Europeans with remote access (LogMAR 0.874 vs 0.577, p<0.001). There was no significant difference in quality of life on completion of the Ministry of Health Impact on Life questionnaire (p-value=0.097).

Discussion

To date, as far as the authors are aware, there are only a small number of studies in New Zealand that have assessed geographic access to healthcare.[9,15,18,19] This study was designed to investigate whether decreased geographic proximity to the referring optometrist, or other demographic variables such as ethnicity, would correlate with worse visual acuity at time of referral for cataract surgery.

Overall there was no statistically significant relationship between geographic proximity to the referring optometrist and visual acuity at the time of referral for cataract surgery. However, driving time and distance to the referring optometrist was on average 27% longer for Māori compared with New Zealand Europeans defined as having remote access. Reduced proximity to optometry services presents a barrier to accessing ophthalmic care that is likely compounded by deprivation and reduced access to transport for Māori with remote access.[15–17] The 2012 Health of Rural Māori Report suggested rural Māori were more than twice as likely to have a 'seeing disability' than non-Māori and half as likely to have seen an optometrist within the last year. Interestingly, this report did not show a difference in 'seeing disability' between rural and urban Māori. This is consistent with our results, where driving distance was not associated with visual acuity.[23]

In the current study, Māori were referred with significantly worse visual acuity and at a younger age than New Zealand Europeans. These results were not explained by geographic proximity. The results align with widespread health inequities between Māori and New Zealand European ethnic groups in New Zealand: a recent large scale study showed that Māori presented on average 10 years earlier for cataract surgery than other ethnic groups with significantly worse visual acuity.[24] New Zealand lacks accurate large-scale epidemiological data on vision loss.[25] Yet cataract accounts for 13% of vision loss in New Zealanders over the age of 40 years,[26] and estimates suggest Māori under the age of 75 are at least twice as likely as non-Māori

Figure 1: Map of the Waikato DHB catchment area. The shortest calculated routes for all patients to their referring optometrist (red markers) are plotted. Routes are colour coded according to driving distance, with lighter colours for longer distances. Māori with remote access (left panel) live, on average, 27% further away from their optometrist and have a higher proportion of lighter coloured routes than New Zealand Europeans (right panel).

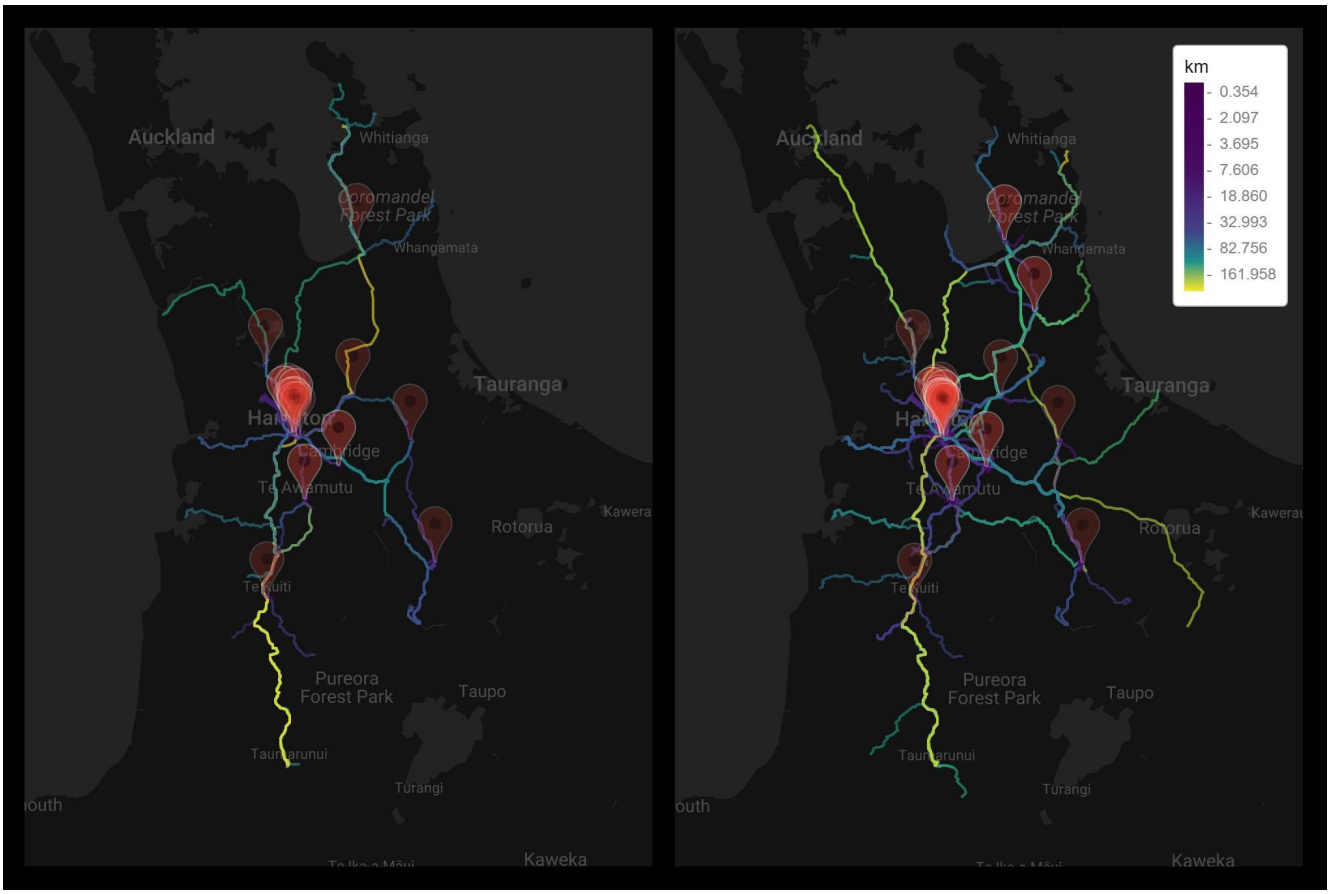


Table 1: Proximity to referring optometrist, visual acuity, and age for each ethnic group.

Ethnicity	**Number** Mean (SD)	**Age (y)** Mean (SD)	**Distance (km)** Mean (SD)	**Driving time (min)** Mean (SD)	**Logmar (worse eye)** Mean (SD)	**Logmar (ou)** Mean (SD)
Māori	148	67.6(11.9)	24.9(33.3)	23.4(26.9)	0.979(0.898)	0.309(0.262)
New Zealand European	961	76.3(11.0)	15.3(24.6)	15.7(19.7)	0.621(0.570)	0.294(0.226)
Other	87	72.7(10.7)	9.4(16.5)	11.7(16.8)	0.691(0.621)	0.246(0.162)
Cook Island	13	64.5(21)	9.34(17.4)	10.8(13.5)	0.955(0.536)	0.278(0.220)
Indian	25	68.2(7.94)	8.77(18.5)	10.9(15.6)	0.972(0.814)	0.340(0.229)
Chinese	14	73.6(8.06)	7.45(20.8)	8.48(17.0)	0.635(0.704)	0.358(0.130)
N/A	12	69.6(6.58)	5.58(7.76)	7.85(6.99)	0.414(0.288)	0.270(0.211)

to have vision loss from cataract, diabetic retinopathy, refractive error, age-related macular degeneration or glaucoma.[26]

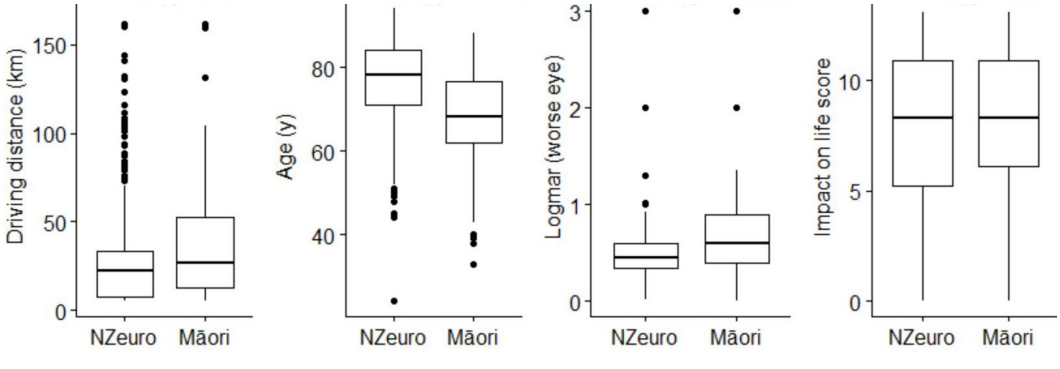
No significant difference was found in quality of life between Māori patients and New Zealand European patients at time of referral. The Impact on Life questionnaire assesses the impact of visual impairment on multiple aspects of the patient's life, as stated in the *Methods* section. This result is surprising given that Māori were noted to have, on average, significantly higher visual impairment than non-Māori. Individuals with visual impairment are 3.5 times more likely than the general population to develop depression and may be at higher risk of accidents, falls and loss of independence.[27–29] The impact of disease on an individual's quality of life is influenced by many factors, including social and economic conditions, personal characteristics and cultural values.[30] Indigenous people, including Māori, are often overlooked in universal measures of wellbeing.[31] Within New Zealand, the utility of cross-population comparison is confined to the measurement of universal aspects of wellbeing (eg, disease prevalence, educational attainment), and measurement of Māori wellbeing necessitates a broader approach that is able to include Māori worldviews.[32]

Optometry practices tend to be concentrated in urban areas, and optometrists in rural and provincial locations have reported difficulty in recruiting both permanent staff and locum cover.[33] Furthermore, in comparison with the total population, a higher proportion of Māori are known to live in small urban areas and rural areas in New Zealand.[34] This aligns with our results, which suggest average driving distance to the referring optometrist is longer for Māori compared with New Zealand Europeans. Further consideration of supply and sustainability of ophthalmic care in rural and provincial towns is needed.[33]

In summary, there does not appear to be a relationship between geographic proximity to the referring optometrist and visual acuity at the time of referral. Perhaps more importantly is that results from the current study highlight inequities in visual impairment and physical accessibility adversely affecting Māori who require cataract surgery. To effectively address these disparities, it is important that healthcare providers routinely test visual acuity and refer early for assessment and treatment of cataract-related visual impairment in Māori.

Health inequities are defined as "differences which are unnecessary and avoidable, but in addition are considered unfair and unjust."[35] Health inequities may arise from differential access to healthcare, differential distribution of the social, environmental, economic and political determinants of health and differences in the quality of care received.[36] The current study is focused primarily on factors impacting access to healthcare. However, it is impossible to completely separate these factors from other causes of health inequity. Although this study focused on investigating geographical access to care, it is important to take a broader view including other factors given that they are likely to contribute to the inequities reported. Māori often experience slower pathways through healthcare and are less likely to visit their optometrist than non-Maori (7.7% vs 12.0%).[37] An identified 'difference in quality

Figure 2: Comparative analysis of New Zealand European vs Māori defined as having remote access (excluding patients <5km from referrer).



of care received' is the screening for and treatment of ischaemic heart disease.[38] More culturally appropriate services with expedited pathways are essential in the New Zealand public health system to effectively address inequities in health for Māori

The current study has several limitations, including its retrospective design and limited sample size. It is likely that the results of this study could not be extrapolated to other regions of New Zealand, where access to healthcare and the proportion of Māori may be different.

Conclusion

To our knowledge, this is the first study in New Zealand to evaluate the physical accessibility of ophthalmic care by calculating driving routes, times and distances. The results are consistent with numerous reports highlighting existing health inequities within New Zealand between Māori and New Zealand European.[26] Māori present younger, and with worse visual acuity, at the time of referral for cataract surgery. Māori who live outside of towns or cities typically have longer driving times to access ophthalmic care and referral to tertiary services within the Waikato District. This represents a potential geographic barrier to accessing care that could be compounded by reduced access to transport. A nationwide study evaluating physical accessibility to ophthalmic care would assist in assessing the need for more rural or mobile healthcare providers in key locations.

Competing interests:
James McKelvie declares: I am a cataract surgeon, consultant opthamologist and CEO of CatRax, a cloud-based pathway management platform for streamlining cataract surgery.

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URL:
www.nzma.org.nz/journal-articles/evaluating-barriers-to-access-for-cataract-surgery-in-waikato-analysis-of-calculated-driving-distance-and-visual-acuity-at-time-of-referral

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Care planning, diagnosis and management in paediatric functional constipation

Darryl J Cochrane

ABSTRACT

Constipation is common in young children and results in approximately 350 hospitalisations per 100,000 population for 0–4-year-olds. Constipation can become chronic in more than one-third of those affected. The purpose of this article is to provide an awareness and highlight the care planning, diagnosis and management in paediatric functional constipation. It is intended for general practitioners and those in primary healthcare who may be unfamiliar with functional constipation. Paediatric functional constipation affects the child's physical, psychological and social wellbeing while causing significant stress to the caregiver/whānau. Despite its prevalence, functional constipation is often misdiagnosed and inadequately treated. Functional constipation requires a comprehensive therapeutic plan, including education, behavioural intervention and medication. Pharmacological treatment often causes concern and misapprehension for developing 'dependence', which is unfounded. Children with chronic constipation who do not progress, despite aggressive medical therapy and behavioural modification, may benefit from further assessment with colonic transit or anorectal and colonic manometry. In the future, novel medical, exercise and surgical strategies will have a role in advancing improved outcomes in children who are unresponsive to conventional medical and behavioural interventions. However, this will require more evidence-based guidelines. Unresponsive constipation cases should be included in the care planning of district health boards, which may assist in a multidisciplinary approach to assisting the physical and psychosocial aspects of constipation.

Paediatric functional constipation is a growing medical condition in New Zealand and worldwide, with a reported average prevalence of 12%[1] (range 0.5% to 32.2%).[2] It accounts for 10% and 25% of admissions in general paediatric and paediatric gastroenterology clinics.[3] In the state of Victoria, Australia, paediatric constipation costs $5.5 million annually,[2] while in the United States the estimation is $3.9 billion,[3] which creates additional financial pressure on burgeoning healthcare systems.

The number of bowel movements varies with chronological age: for instance, 5–40 motions per week are regarded as the normal range for a 3-month-old, and 4–20 and 3–14 motions per week for 12-month- and 3-year-olds, respectively.[4,5] According to Yacob et al, constipation onset can occur at three different stages.[3] It can occur from (1) the transition from breast-feeding or formula milk to solids, (2) toilet training or (3) the commencement of day care, kindergarten or school. Functional constipation is distinguished by painful bowel movements, irregular defecation, extreme stool retention and large stool calibre.[3] It may also include faecal incontinence that is caused by the overflow of soft stools around a hard and large faecal deposit accumulated in the rectum.[6]

The aetiology of functional constipation remains unclear, although nutritional, behavioural and psychosocial abnormalities and genetic factors may be contributing factors.[7] More than 33% of children develop chronic symptoms where pain is an important aspect in prompting fear and the withholding of defecation. It has been reported that 50% of children with

functional constipation have persistent symptoms after 6–12 months of conventional treatment and 25% have symptoms that continue into adulthood.[8] Despite these realities, the majority of children with functional constipation do not receive timely treatment.[9] Predicting which children will benefit from treatment is difficult due to inconsistent prognostic factors.[8]

Care planning

Care planning focuses on patient-centred care that considers the needs, concerns, beliefs and goals of the person rather than the needs of the systems or professionals.[10] It is underpinned by shared decision-making and communication to support behaviour change and improve health knowledge. Typically, a care plan includes assessment, diagnosis, prioritised interventions, medical management, key actions and tasks, role responsibility, crisis or contingency planning and times and methods for review and follow-up. There are various paediatric constipation care plans, some of which are complex and others simplistic (Figures 1 and 2).

The benefit of a care plan is to enable and improve communication between the patient and healthcare team in real time. There are various generic hard copy and electronic care plans that are available on the Health Navigator New Zealand website.[11] Increasingly, web-based and electronic tools are being used to document care plans and are usually part of an extensive patient system that may include a patient portal.[11] The majority of New Zealand district health boards (DHBs) will have a child constipation care plan that will be based on high-quality information and known national and international best practice guidelines. The contributors to these plans work in the clinical setting and have expertise and specialisation in paediatric medicine. Thus DHBs' care plans may differ slightly depending on the local expertise.

Practitioners can access their local DHB care plan through Community HealthPathways website. The care plan should include the definition of chronic constipation, the age range that the plan is for and criteria to thoroughly assess the patient's history (ie, onset of constipation, frequency and type of stools, soiling, bleeding, pain with stool, diet, exercise, abdominal pain). The clinical assessment should include height, weight, nutritional status, abdomen, spine and lower limbs (muscle tone, reflexes, gait) and perianal conditions (fissures, fistula, lipoma). An abdomen x-ray is not required. Blood mixed within a stool and vomiting in the setting of faecal impaction requires urgent referral.[12] The care plan should include guidelines for disimpaction (prescription), management (medication, diet, behavioural, exercise, toileting) and ongoing management, whether or not the child responds over the defined duration.[12] A constipation care plan may also include red flags (eg, when the child is unwell and has any of the following: greater than 48 hours delayed passage of meconium or symptoms within two weeks of birth, passage of toothpaste or ribbon stools, abdominal distension and vomiting, abnormalities of anus, spine or gluteal region, unexplained weakness or deformity of lower extremities, neurological findings and weight loss or faltering growth).[13]

Recent international research identified that a paediatric constipation action plan (AP) requires key evidence-based concepts, including imagery, comprehension, quality, readability and suitability using jargon free language.[14] The researchers investigated the use a pictogram-based constipation AP to assist clinicians, caregivers and children in the management of functional constipation (Figure 3).[14] The AP was designed to optimise knowledge transfer between the health service and caregiver at the time of discharge and empower home management of constipation. The AP adopted a health-informed approach to provide information on evidence-based medication and behavioural interventions, and to reduce disparities in constipation outcomes related to low health literacy.

The AP included four sections:

1. Cleanout: green (feeling good).
2. Maintenance: yellow (feeling bad).
3. Acute: red (feeling worse).
4. Severely acute.

Each section included the type, amount and frequency of medication, with key behaviours highlighted in the green, yellow and red sections. According to the authors, the twelve images in the pictogram were easily interpreted and facilitated compre-

hension for patient and caregiver. Using lay language with the images maximised the caregivers' comprehension, which further empowered caregivers to improve their child's compliance and clinical outcomes.[14]

In New Zealand, the Auckland Region Community HealthPathways has compiled a constipation AP[15] with the aim for children to pass at least three soft, painless bowel motions per week (type 4 stool). The AP includes a YouTube video link on constipation and conveys to the caregiver key bullet points about providing three servings per week of foods containing seeds (kiwifruit) or segments (mandarins), increasing fibre and water intake, encouraging regular exercise and practising regular and good toilet technique. It also provides a disimpaction plan (similar to the Waitematā DHB schedule[16]), regular maintenance medication prescription and a stool dairy for monitoring bowel movements, to assist the caregiver and child with the progress and the medical staff in determining the correct treatment. Finally, a reward star chart is included to motivate and encourage positive behaviour from the child.

Diagnosis

Rome IV[17] provides a method for diagnosing functional constipation, according to which two or more criteria must occur one or more times per week for a minimum of one month (Table 1). It is important that a thorough and correct assessment is undertaken. This should include a physical examination to assess the abdomen for faecal masses, anal patency, anal fissures and patulous anus, as well as neurological testing for reflexes, lower-limb tone, spine and gait.[5] Further examination should

Figure 1: A New Zealand example of a paediatric constipation care plan.

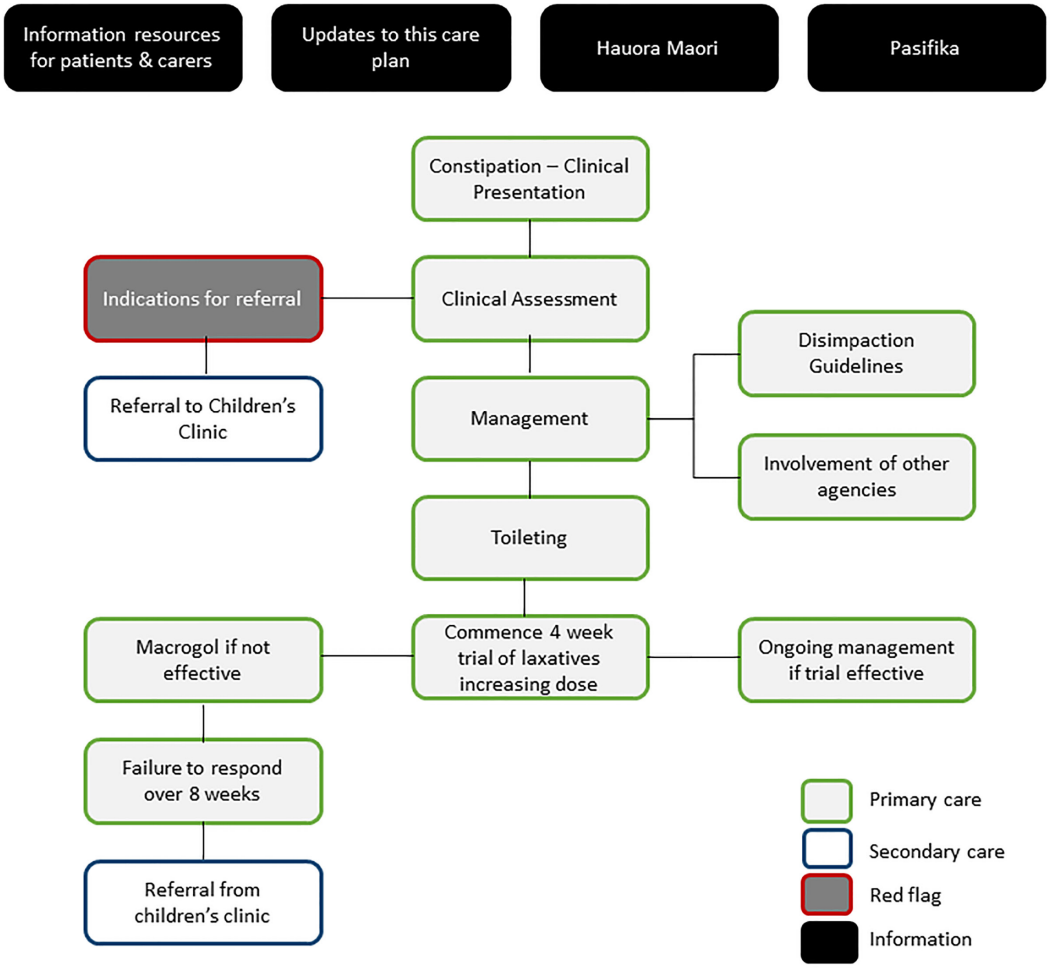

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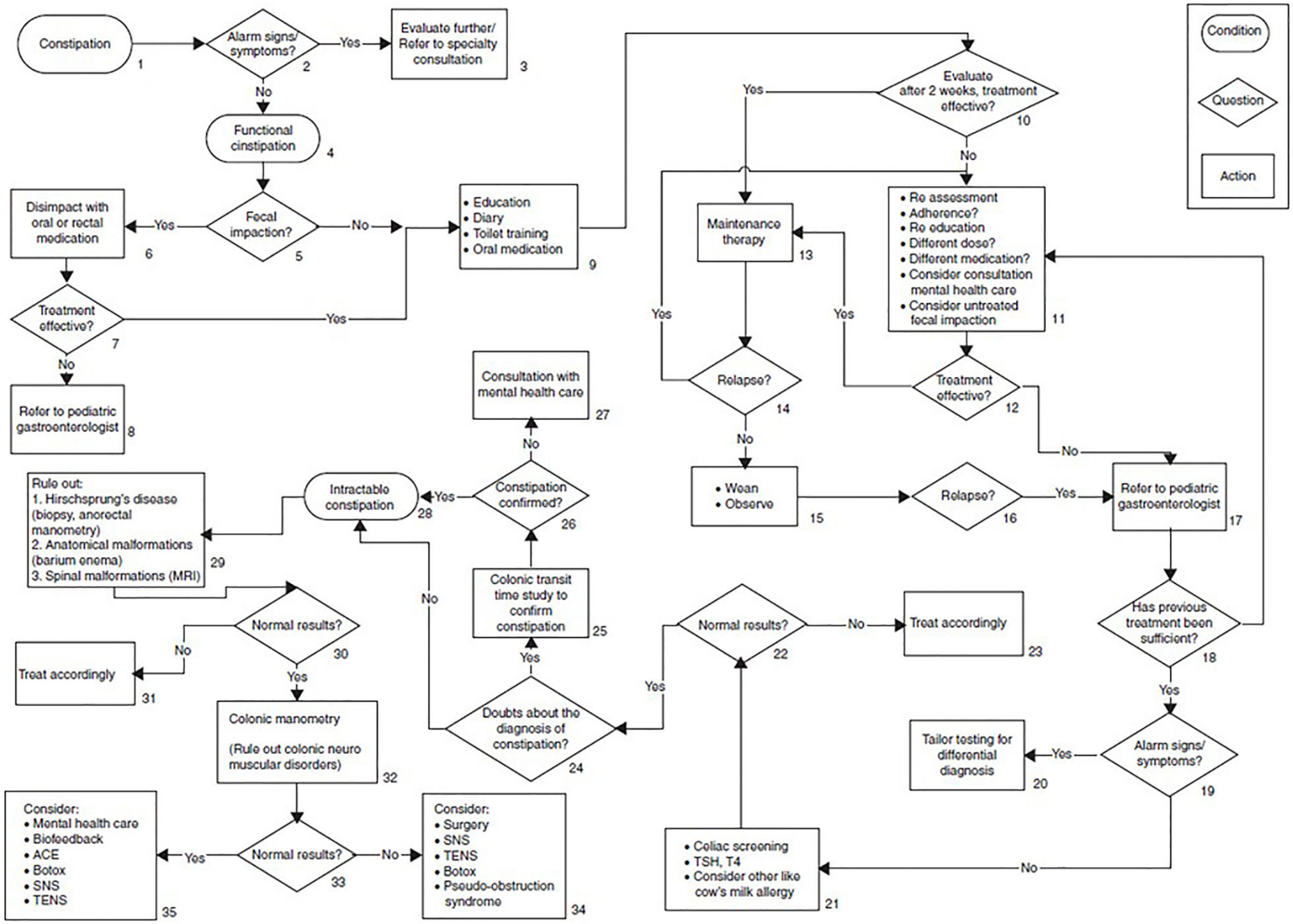
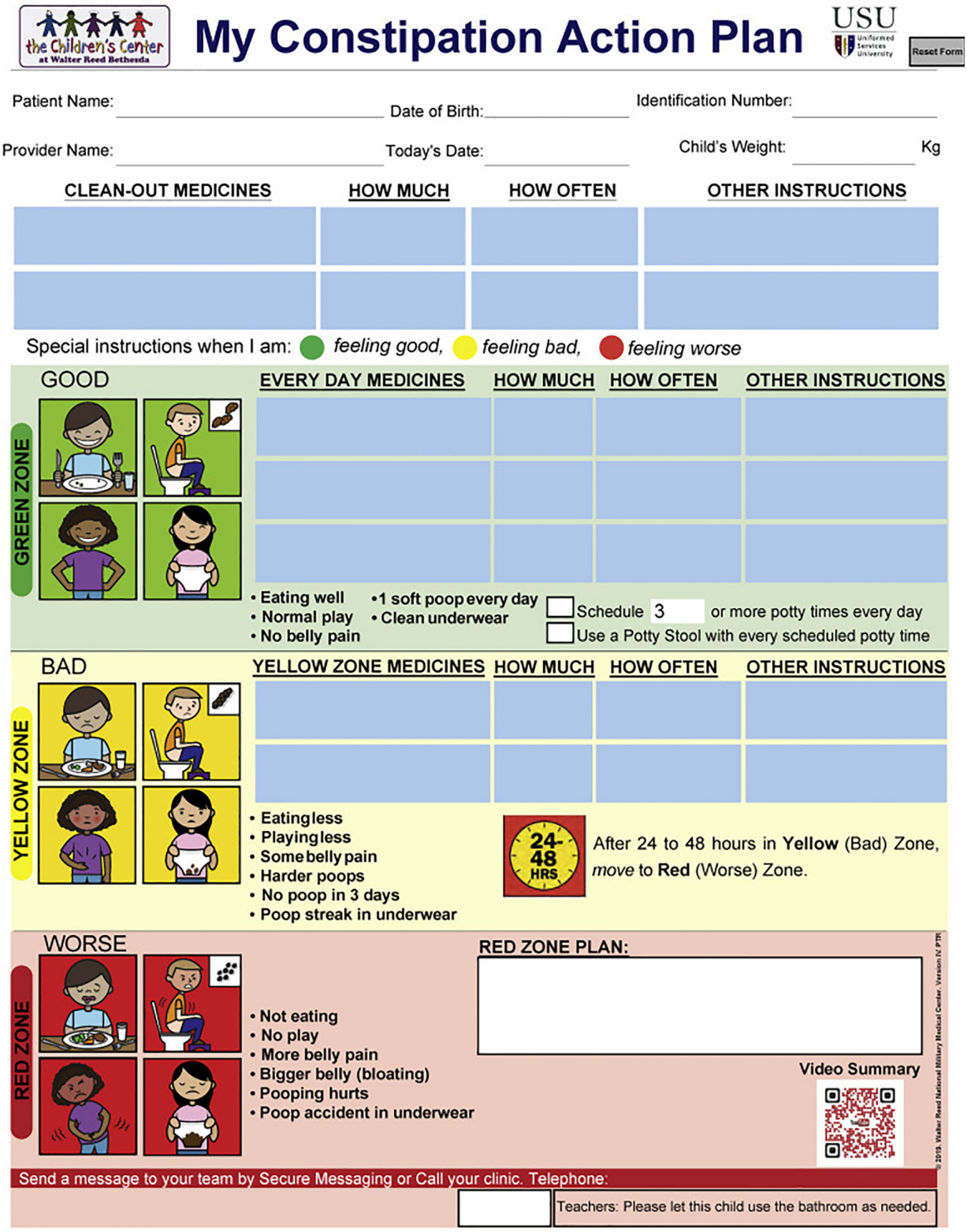
Figure 2: An international example of a paediatric constipation care plan for infants 6 months of age or older.[6]



ACE = antegrade continence enema; MRI= magnetic resonance imaging; SNS = sacral nerve stimulation; TENS = transcutaneous electric nerve stimulation; TSH = thyroid-stimulating hormone.

Figure 3: An international example of an action plan for paediatric functional constipation.



identify or discard other underlying pathophysiology, such as perianal disease, Hirschsprungs disease, inflammatory bowel disease, urinary symptoms and systemic symptoms (reduced body mass, decline in growth, lethargy).[5] Laboratory testing should only be performed to exclude an underlying condition such as hypothyroidism or hypercalcaemia. Coeliac disease, associated with iron deficiency anaemia, abdominal pain and poor growth, should be considered for assessment if constipation arises early with the introduction of gluten.[6]

Due to its poor reliability, abdominal radiography is not recommended for diagnosis.[1] However, there are exceptions: for example, when a child's history is unclear, when confirming faecal impaction or when planning treatment for disimpaction.[3] In cases with a history of chronic constipation, anorectal manometry can assess anal sphincter function, pelvic floor function and anorectal reflexes. When the constipation is severe and unresponsive to conventional treatment, colonic manometry is used to assess colon motility.[3] Magnetic resonance imaging is not advised in the absence of neurological abnormalities.[6] Other diagnostic techniques include colonic transit time, scintigraphy, rectal barostat and wireless motility capsule.[1]

Management

The treatment plan should include a holistic team approach involving the paediatric clinician, paediatric continence nurse, parents, whānau, dietician, clinical psychologist, physiotherapist and, when required, Māori and Pacific health specialist staff. The common approach to treating functional constipation is education, behavioural modification and laxatives.[3] In New Zealand, when paediatric constipation is more severe and treatment is unresponsive, there may be an underlying condition. The general practitioner will refer the child to a continence service or paediatric department of the local DHB. Under a paediatric continence nurse-led intervention, the nurse works in close co-operation with the consultant paediatrician to determine a treatment plan. The paediatric continence nurse also works closely with the caregiver by providing regular telephone follow-ups. This close communication allows for ongoing medical management, reduces emotional stress and provides reassurance to the caregiver of the long-term plan for their child. The approach of a nurse-led intervention is considered internationally an effective use of services and cost-efficient in providing greater care for paediatric constipation.[18]

Depending on the severity and longevity of the constipation, some caregivers become frustrated with the lack of therapeutic diagnostic testing, which can unpropitiously affect the treatment due to misunderstanding and noncompliance. It is imperative that the medical team provide clear and succinct written and verbal communication about the diagnosis to the caregiver. The medical team should focus on all treatment being individualised and long-term. Therefore, it is important that caregivers follow the instructions given to them by the medical team and enact the treatment plan. Central to the plan is the caregiver's ability to be educated. This requires time and effort to bring a positive change. In addition, caregivers are encouraged to provide healthy, well-balanced meals with adequate fibre to soften the stool consistency. Increasing fibre also requires increasing the child's water intake. The action plan (Figure 3) is a key document

Table 1: Rome IV constipation criteria.

• Two or fewer defaecations
• At least one episode of faecal incontinence
• History of retentive posturing or excessive volitional stool retention
• History of painful or hard bowel movements
• Presence of a large faecal mass in the rectum
• History of large diameter stools that may obstruct the toilet
• Symptoms occurring at least once per month for a minimum of one month, with insufficient criteria to diagnose irritable bowel syndrome

in assisting with monitoring, treatment and ongoing care of the child.

Diary

It is imperative caregivers complete a daily diary on the amount of medication, frequency and type of stool (using Bristol Stool Form Scale), associated behaviours, fluid intake and food intake. The recording of data can be tedious and a burden for the caregiver, but it is an invaluable source of information for the medical team to determine the defecation pattern, quantify therapeutic progress and enhance treatment adherence. Various mobile applications (apps) currently exist (Stool Log—Bowel Movement Journal, GutTracker, Poop Tracker, PoopLog) that allow the user to track and analyse bowel movements. PoopMD+, a mobile app that uses a smartphone's camera and colour-recognition software to analyse an infant's stool, can accurately identify images of pale-coloured stools.[19] However, a comprehensive, cloud-based diary app that includes the aspects described above should be developed. This would expedite data entry, increase compliance and allow proactive monitoring, diagnosis and treatment, which would benefit both the caregiver, child and medical team.

Toilet training

It is often difficult to undertake toilet training when a child has functional constipation. Out of despair of trying, some caregivers abandon toilet training, which they later regret because their child may not become toilet trained before starting school. This can cause distress for both caregiver and child. For children not toilet trained, it may be appropriate to continue with nappies. Toilet training should be encouraged when laxatives have softened the stool and the child has regained confidence . Caregivers need to create a non-threatening and pleasant environment. This requires patience, consistency, regularity and encouragement. A child may have increased anxiety when using toilets outside their home, which further increases the likelihood of withholding. A study revealed that school toilets were an unpleasant, terrifying place where bullying occurred, which is likely to exacerbate withholding.[20] Using the toilet requires comfort, safety and appropriate ambience. Day-care centres, kindergartens and schools may need to address the state and environment of their toilets.

The rectum ampulla stores the stool and expands the rectal walls, which stimulates the stretch receptors. This sends a message to the brain indicating that it's toilet time. The problem occurs if the child decides to withhold; as the stool sits in the rectum, water continues to be absorbed by the colon and the stools become very hard, and as more food is digested, additional stools fill the rectum and it backfills into the colon. When the child eventually visits the toilet, the stool is very hard and large, which makes it difficult to pass. Therefore, it is beneficial to establish a toilet-training routine. Regularity is important for toilet training. Children should be encouraged to sit on the toilet at frequent periods: for example, it is preferable to schedule using the toilet 20 minutes after a meal,[21] and following breakfast and dinner is considered the best time.[13] Encouraging and praising the child are important aspects for successful toilet training. Incentives, such as star charts, new underwear or special 'treats', may help to reinforce positive behaviour.[13,21] It is important that the child performs correct toilet posture. This means knees higher than hips (use a footstool), elbows on knees, leaning forward, pushing the abdomen out and straightening the spine.[13,21]

Medication

Many caregivers have concerns about the frequency and amount of prescribed medication. Laxatives are essential for the treatment of constipation as they re-establish regular, painless bowel movements,[5] so that the enlarged rectum can return to a normal size. The aim of the medication is to soften the stool. Common laxatives include lactulose, docusate tablets, magnesium hydroxide or macrogol. Magnesium hydroxide (8%) is a mixture that pharmacists need to prepare before being dispensed, and it is not recommended for long-term use unless under medical supervision.[22] Macrogol-3350 (Molaxole®, Movicol®, Movicol®-Half, Lax-Sachets®) is a powder that gets mixed with liquid. Each sachet of macrogol contains 13.125 g and electrolytes. Stimulant laxatives, such as bisacodyl, glycerol, poloxamer 188 and sodium picosulfate, are effective in gener-

ating propagated colonic contractions. At certain times, these strong and sustained colonic contractions can be interpreted as abdominal cramping. Some children have a negative response to this cramping sensation. They may complain, withhold and misuse the opportunity to have a bowel movement. It is important that caregivers are aware of the cramping, and if the cramping is severe, the dose may need adjusting.[3]

For disimpaction, a high dosage and large volume of liquid consumption is required until the bowel is emptied. Initially, macrogol is prescribed for disimpaction. If there is no response to macrogol, sodium picosulphate can be considered.[13] An alternative method to delivering the powerful laxative solution is a nasogastric tube, which requires hospitalisation for approximately seven days. The procedure of the nasogastric tube can be a terrifying experience for both child and caregiver. Recently, a 3-year-old diagnosed with faecel impaction rejected the nasogastric tube by vomiting its displacement, causing severe distress and anxiety to both child and caregiver. Oral treatment of macrogol is advised when possible. However, this relies on the child consuming the prescribed liquid, which is sometimes difficult to achieve. International research for disimpaction recommends a dosage 1–1.5 g/kg/day for 3–6 days.[23] In New Zealand, Waitematā DHB recommends different dosages for children aged 2–5 years and 6–11 years (Table 2).[16] This is based from the Movicol Junior® disimpactment dosage approved by Medsafe.[24] Maintenance therapy for macrogol ranges from 0.75 g/kg/day[25] to 1 g/kg/day.

If faecal impaction is untreated, the overall treatment for constipation will be ineffective. The prescription of laxatives will require ongoing adjustment (higher or lower) depending on the child's response to the medication. The duration of laxatives often ranges from months to years rather than weeks.[22]

Most laxatives have a disclaimer that prolonged use is not usually recommended and may lead to dependence. This heightens a caregiver's apprehension about their child's long-term medication use. Although the chronic effects have not been extensively investigated, the bowel does not become 'dependent' on the medication.[26] The benefits of pharmacologic treatment outweigh its potential adverse effects, and the concern of developing dependence is unfounded.[3] Medicating for a soft stool will allow the bowel to return to its normal size, shape and function. This requires medication to be administered regularly for a prolonged time and caregivers should therefore remain attentive to the treatment plan.

Other treatments

Functional constipation may require multidisciplinary treatment, but currently there is a lack of evidence to support this.[6] Novel therapies, such as sacral nerve stimulation, have yielded positive results and may be considered in the overall treatment plan. Research reported that six months of transcutaneous electrical stimulation treatment significantly improved defecation frequency, soiling, abdominal pain, urge to defecate and quality of life in 50% of children with chronic constipation.[27] Greater research is required to confirm its use. Other therapies of pre- and pro-biotics are considered ineffective in treating paediatric constipation.[6] A normal fibre intake is recommended and can be achieved with at least three servings each of fruit and vegetables, selecting wholemeal bread and cereals high in fibre, adding bran to baking and including legumes. There is no evidence to date to

Table 2: Recommended dosage for child faecal disimpaction.[16]

Age (years)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
2–5	1	2	2	3	3	4	4
6–11	2	3	4	5	6	6	6

support the use of fibre supplements to treat functional constipation, and allergy testing is not recommended for diagnosing suspected cow's-milk allergy in children with constipation.[6]

It is unclear whether physical activity assists with constipation. Physical activity was associated with a reduced risk of functional constipation in pre-school-aged children. [28] But, in contrast, a higher level of physical activity was observed in preadolescent children diagnosed with functional constipation.[29] Expert opinion recommends a normal level of physical activity for children with constipation.[6] In New Zealand, it is recommended that toddlers and pre-schoolers disperse at least three hours of physical activity across each day,[30] and that 5–17-year-olds accumulate at least one hour a day of moderate to vigorous physical activity, plus strengthening activities at least three days a week.[31]

The use of physiotherapy treatment remains equivocal. Six weeks of physiotherapy treatment involving muscle training of the abdominals, breathing exercises and abdominal massage improved the frequency of bowel movements compared to the medication group.[32] Similarly, an eight-week programme focused on pelvic floor muscles reported a significant increase in stool frequency and stool diameter, but no changes were observed in stool withholding, faecal impaction and defecating pain.[33] A recent study, however, reported that after eight-months of combining physiotherapy treatment activating abdominal and pelvic floor muscles with conventional treatment (toilet training, nutritional advice, laxatives) was not effective compared to conventional treatment alone.[34]

Surgical intervention

Despite aggressive therapy of high-dose laxatives and behavioural modification, some children with chronic, intractable constipation do not progress. Intractable constipation is defined as not responding to optimal conventional treatment for at least three months.[6] It can become so severe that it adversely affects the child's self-esteem and ability to socialise, which impacts the quality of life of the child and family.[35] Surgical intervention is considered a treatment of last resort, but it may be advised in difficult intractable cases. The type of surgery will be determined by a comprehensive evaluation of the colonic and anorectal anatomy and physiology, and anorectal and colonic manometry are often used to guide surgical decision-making.[36] Surgical strategies vary across New Zealand. They are limited to a number of regions and are not available to the primary care physician. A survey of physicians specialising in paediatric surgery and paediatric gastroenterology reported considerable variation in the diagnosis and treatment of children with intractable constipation. The authors of the survey suggested there is a great need for evidence-based guidelines for children who respond inadequately to pharmacological management.[36]

In summary, constipation is a chronic condition and its treatment requires medication to keep the stool soft and behavioural interventions. A thorough history, including questions about the frequency of bowel movements and stool type, is required. If no red flags are found after examining the abdomen, spine, lower limbs and perianal area, the practitioner should have confidence to aggressively manage the constipation[37] through a constipation action plan.[15,37]

Competing interests:
Nil.

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Participant injury in clinical trials conducted in New Zealand for the benefit of manufacturers: an unfair system?

Mark J Bolland

ABSTRACT

A patient with a long-standing medical condition was enrolled in a clinical trial, deemed as conducted for the benefit of the manufacturer. The patient entered the trial and, shortly afterward, developed a severe illness that left him with a significant permanent disability. Clinical investigators and clinicians not involved in the trial believed the illness was related to trial participation. Because the trial was for the manufacturer's benefit, the participant was not eligible for compensation from the Accident Compensation Corporation (ACC). Discussions with the trial sponsor took many years to resolve. This case highlights the numerous barriers faced by patients seeking compensation from trial sponsors for adverse events probably resulting from trial participation. Legal changes are required to resolve this situation. Without such changes, potential participants and researchers should consider carefully whether to participate and invite people to participate in trials conducted for the benefit of a manufacturer, as there may be little support available should a trial-related illness occur.

In New Zealand, participants in clinical trials that are deemed as being conducted for the benefit of the manufacturer are not eligible for Accident Compensation Corporation (ACC) coverage if they suffer an injury from participating in the trial. At ethics committee submission, investigators indicate whether the trial is conducted for the benefit of the manufacturer, and the ethics committee confirms that they are in agreement with that view during the approval process. Here I outline a case that highlights many problems with the current process and discuss potential solutions.

Case details

A middle-aged man was referred for a specialist review to help control a long-standing medical condition. Before that review, he was approached to participate in a clinical trial. He agreed, entered the trial, received the study medication, but unfortunately suffered a significant illness that led to him being withdrawn from the trial. The physicians involved believed the illness was related to participating in the trial, and he was referred to a medical outpatient clinic for ongoing management.

The illness had an enormous impact. Although he made a slow initial recovery, his health never returned to baseline levels and he remained severely affected and persistently disabled over the next several years. He required time off work, changed his job, reduced his work hours, but ultimately was no longer able to work. He could no longer drive a car, had to move to a house more suitable for his poorer physical condition, and was unable to carry out the usual daily and leisure activities he previously undertook. There was a large amount of emotional stress and financial pressure, both for him and for his extended family. Family members moved cities to live nearby and provide support. Collectively, there was a substantial reduction in quality of life and a restriction of lifestyle.

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Support and compensation

The clinical trial was deemed as being conducted for the benefit of the manufacturer, and therefore participants were not eligible for ACC coverage if they were to suffer an injury that resulted from participating in the trial. Because the clinicians involved had assessed his injury as being related to trial participation, he was ineligible for ACC coverage. The patient was therefore advised to seek support and compensation from the trial sponsor. The ineligibility for ACC coverage is not a criticism of ACC or its processes. The case was not reviewed by ACC (and therefore was not declined for coverage by ACC) because it was felt that the relationship of the injury to the trial participation precluded him from ACC coverage.

A claim was lodged with the trial sponsor. There was disagreement with the assessments of the treating clinicians and the sponsor denied liability and rejected the claim. Subsequent discussions with the sponsor were prolonged, lasting more than six years. While the discussions took place, the participant did not receive any support or assistance with his illness or subsequent disability from the trial sponsor.

The participant required legal support for these discussions, which he could not afford. The precise details of the case and the discussions with the trial sponsor remain strictly confidential and are unable to be discussed in greater detail for legal reasons. Nevertheless, the details provided illustrate problems with the compensation process for trial participants. Table 1 highlights some of these issues and other barriers faced by trial participants attempting to seek support or compensation if they are ineligible for ACC coverage.

Informed consent?

Table 2 shows the relevant sections of the information sheet and consent form signed by the participant. The information provided to the participant about treatment and compensation for injury is clearly inconsistent with the subsequent events. For example, there is the clear undertaking, albeit not legally binding, that if an injury is related to the trial, compensation comparable to ACC coverage will be provided. Furthermore, there is no suggestion that the participant would be required to prove an illness was causally related to the trial medication, as the trial sponsor has required. Given the marked inconsistency between the information provided in the consent form about injury and the participant's experience, it is reasonable to conclude that the information provided was inadequate, and therefore truly informed consent was not obtained.

The text used for this information sheet was the standard text provided by the New Zealand ethics committees at the time for use in all clinical trials deemed to be conducted for the benefit of the manufacturer. Subsequently, the text was updated in 2015 and 2018. Table 2 shows that the 2015 text was considerably briefer and again inconsistent with the trial participant's experience. The 2018 text is considerably more detailed and more cautious. However, parts are still confusing: initially the text states that New Zealand guidelines require compensation to be at least ACC equivalent, but later contradicts this statement by saying industry guidelines may not provide ACC-equivalent compensation. It seems unlikely that potential participants would truly understand the significance of the text or that, if they were to be injured during the trial, they may face as daunting a process as the one outlined in this article.

Law, ethics and compensation in commercial trials

Professor Jo Manning has recently conducted detailed reviews of the ethical and legal aspects of compensation in clinical trials conducted in New Zealand. Some of the key points and conclusions from these reviews are summarised here (for details and references see Manning J[1] and Manning JM[2]).

Research participants were covered by ACC until 1992, when legislation was passed that excluded participants in commercial trials from ACC coverage. The rationale was that, because commercial companies profit from medicines trialled, they should meet the costs of compensation for injuries during the trials rather than the ACC-levy payers. However, this left a gap in compensation coverage for participants in commercial

Table 1: Problems in the process of seeking compensation from the trial sponsor.

Problem	Issues
Lack of equity	Denied access to standard care, support and compensation that other trial participants receive from ACC. Rehabilitation and support may not be offered by the trial sponsor immediately after the illness, which is when support is needed (and as would normally be available through ACC).
Unreasonable delays	Process is prolonged. In this case, it took over six years to resolve.
Unreasonably high requirements for proof of causality	Processes place burden of proof on participants to prove their illness is causally related to trial participation, without similar a requirement for trial sponsors to provide proof of the corollary—that the illness would have occurred if the patient had not participated in the trial.
Lack of suitable resources	Trial participants have few independent experienced resources to assist them: in this case the Health and Disability Commissioner declined to assist; it was unclear where else to turn.
Lack of experienced assistance in New Zealand	Because ACC coverage extends both to complications of treatments that are not a "necessary or ordinary consequence" of the treatment and trials not done for the manufacturer's benefit, few practitioners have experience of such cases. In this case, numerous specialists declined to provide expert opinions.
Reliance on legal opinion	Legal counsel is rarely required in New Zealand healthcare, but mediation with legal assistance from an early stage is a central component of the process.
Financial burdens	Legal counsel is very expensive and, in this case, was unaffordable in the context of an illness that had already placed a huge financial burden on the trial participant.
Unfair mediation process	Any result from a mediation process is non-binding, according to the industry guidelines that pharmaceutically sponsored clinical trials are conducted under.
Inequity in resources	The process is adversarial, with a single trial participant placed against a multinational company that has greater financial resources and access to expert witnesses and legal representation.
Process inconsistent with Medicines New Zealand guidelines	Medicines New Zealand "favours a simple and expeditious procedure in relation to the provision of compensation for injury caused by participation in clinical trials."[3] The case demonstrates the process is neither simple nor expeditious.
Confidential agreements	Potential trial participants and researchers can be unaware of issues related to seeking compensation or how commonly these difficulties arise.

Table 2: Relevant sections of trial information sheet and consent form and templates from the New Zealand Health and Disability Ethics Committees.

Text from information sheet and consent form signed by participant *Treatment and Compensation for Injury* The Ethics Committee has certified that this clinical trial is being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which this trial is being carried out. This means that if you suffer injury as a result of your participation, you will not be eligible for cover under accident compensation legislation. However, if you follow the directions of the doctors in charge of this study and you are physically injured due to any substance or procedure given to you in accordance with the plan for this study, [the trial Sponsor] will pay the medical expenses for the treatment of that injury which are not covered by your medical insurance or by any other third party in accordance with the "New Zealand Researched Medicines Industry Guidelines on Clinical Trials- Compensation for injury resulting from participation in Industry Sponsored Clinical Trials". Those guidelines say that compensation should be no less than would be awarded under the accident compensation scheme. These RMI Guidelines are only guidelines and until your claim is assessed by the insurers of [trial Sponsor] and Company (NZ) Limited, it cannot be said with any certainty exactly what type or amount of compensation you will receive if you suffer injury as a result of your participation, or what sort of injury will be covered. The guidelines require that compensation must be provided by [trial Sponsor], where the injury you suffer is serious and not just temporary and is one caused by the trial medicine or item or where you would not have suffered injury but for your inclusion in this trial. The guidelines also require that the compensation you receive must be appropriate to the nature, severity and persistence of your injury. This means that you may not receive compensation from [trial Sponsor] if your injury is minor or temporary. Further, you may not receive compensation from [trial Sponsor] if your injury was caused by the investigators, if there is a deviation from the proposed plan of research, or if your injury was caused solely by you
Suggested text from consent form template 2015 If you were injured as a result of treatment given as part of this study, which is unlikely, you won't be eligible for compensation from ACC. However, compensation would be available from the study's sponsor, [x], in line with industry guidelines. We can give you a copy of these guidelines if you wish. You would be able to take action through the courts if you disagreed with the amount of compensation provided. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

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Table 2: Relevant sections of trial information sheet and consent form and templates from the New Zealand Health and Disability Ethics Committees (continued).

Suggested text from consent form template 2018

As this research study is for the principal benefit of its commercial sponsor [insert name], if you are injured as a result of taking part in this study you won't be eligible for compensation from ACC.

However, [insert name] has satisfied the [insert name] Health and Disability Ethics Committee that approved this study that it has up-to-date insurance for providing participants with compensation if they are injured as a result of taking part in this study.

New Zealand ethical guidelines for intervention studies require compensation for injury to be at least ACC equivalent. Compensation should be appropriate to the nature, severity and persistence of your injury and should be no less than would be awarded for similar injuries by New Zealand's ACC scheme.

Some sponsors voluntarily commit to providing compensation in accordance with guidelines that they have agreed between themselves, called the Medicines New Zealand Guidelines (Industry Guidelines). These are often referred to for information on compensation for commercial clinical trials. There are some important points to know about the Industry Guidelines:

On their own they are not legally enforceable, and may not provide ACC equivalent compensation.

There are limitations on when compensation is available, for example compensation may be available for more serious, enduring injuries, and not for temporary pain or discomfort or less serious or curable complaints.

Unlike ACC, the guidelines do not provide compensation on a no-fault basis:

The Sponsor may not accept the compensation claim if:

Your injury was caused by the investigators, or;

There was a deviation from the proposed research plan, or;

Your injury was caused solely by you.

The injury was caused by <<NAME OF COMPARATOR DRUG>> (include only if holds true for specific study)

An initial decision whether to compensate you would be made the by the sponsor and/or its insurers.

If they decide not to compensate you, you may be able to take action through the Courts for compensation, but it could be expensive and lengthy, and you might require legal representation. You would need to be able to show that your injury was caused by participation in the trial.

You are strongly advised to read the Industry Guidelines and ask questions if you are unsure about what they mean for you.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

trials. An industry body, the Researched Medicines Industry (now known as Medicines New Zealand (MNZ)), adapted UK guidelines for compensation, which were then adopted for use in New Zealand.[3]

The key drawback of these guidelines is that a sponsor's obligation to pay compensation for research-related injury is expressly stated to be 'without legal commitment' (ie, legally unenforceable by the injured participant). There have been repeated calls to repeal the section of the Accident Compensation Corporation Act 2001 (the ACC Act) that excludes commercial trial participants from coverage. In 2007, the chairs of the ethics committees, and in 2010 and 2014 the National Ethics Advisory Committees, called for repeal or review of this provision, but this was not acted on by the Government in 2015 after consideration by the Minister for ACC and the Minister of Health.

There is general agreement that no-fault compensation is the best ethical response to research-related injury. The alternative, adversarial approach presents formidable barriers to trial participants, who are usually required to prove both negligence, which is unlikely to have occurred, and a causal link between the injury and the treatment received, which is difficult to establish.

The MNZ guidelines have been criticised for a number of reasons. Not all trial sponsors are members of MNZ and use these guidelines. And even when used, the guidelines are not legally enforceable, lack specific details about the quantum of compensation (other than a broad statement that they should be at least ACC-equivalent), lack details of the time frame within which claims should be resolved and contain numerous exceptions when compensation will not be paid. If there is disagreement between the injured participant and the trial sponsor, mediation at the sponsor's expense is offered but the results are non-binding. Overall, these industry-developed and industry-sponsored guidelines are considered to be heavily weighted in favour of trial sponsors.

On the basis of these extensive reviews,[1,2] Manning concluded that these compensation arrangements for trials deemed as being conducted for the benefit of a manufacturer fall below ethical expectations. In particular, the main issues are that the compensation process followed is only a 'guideline'; there is no legal obligation on the sponsor to pay compensation; the process of obtaining compensation is weighted against the participant and will be insurmountable for the majority of participants; and information sheets provided to participants do not provide adequate information, such that injured participants will only find out the true situation when they come to submit a claim.

A possible solution?

An alternative to the current process is that all injury in all trials should fall under ACC coverage, regardless of whether the trial is conducted for the benefit of the manufacturer. In practice, one potential approach would be that prospective trials are assessed by ACC (at sponsors' expense), and that a levy is charged according to the risk of the trial and number of participants. Potential cases of injury would then be handled through existing ACC protocols. Claims would be directly submitted to ACC and resolved between ACC and the trial participant. The trial sponsor would be informed by ACC of the outcome. This approach would address many of the problems identified in Table 1 and provide trial participants with the confidence they will be dealing with ACC, a respected New Zealand Crown entity, rather than facing potentially adversarial dealings with a multinational company.

Another approach could be that, instead of charging a levy, ACC assesses injuries through existing processes, and if an injury meets criteria for ACC support and/or compensation, it would be provided by ACC and the costs passed directly to the trial sponsor.

Manning reviewed possible improvements to the current system and the legal issues related to such solutions, concluding that the best and simplest legal option is repeal of the relevant section (32 (6)) of the ACC Act that excludes personal injury suffered by a participant in a commercially sponsored trial. This would mean that all trial participants are covered by ACC, as outlined in the previous paragraph. The advantage for trial participants is fairer access to superior compensation than the current system offers. The main concern for trial sponsors is that this would set a worldwide precedent for managing possible trial-related injury, but this is unlikely given the unique nature

of the ACC scheme. The main concern for regulators is that this approach may shift the risks and costs of trials from the trial sponsor on to ACC, leading to riskier trials and greater costs for ACC. In practice, this seems unlikely to occur, because if an ACC levy were charged at market rates, the levy would probably be similar to or higher than the insurance premiums that trial sponsors are currently required to pay.

Manning also considered other alternatives, such as participants making a legal claim against the company, providing better informed consent, requiring ethics committees to refuse to provide approval unless appropriate compensation processes are in place, or requiring sponsors to purchase ACC coverage for the trial. However, Manning considered that none of these options were as simple, timely or likely to be as effective as repealing the provision in the ACC Act that excludes commercial trial participants from coverage.[1,2]

Returning to the case. If the trial had been publicly funded or if commercial trials fell under ACC coverage as proposed, the participant would almost certainly have been covered and compensated by ACC because injuries that are not a necessary or ordinary consequences of the treatment being trialled are covered; compensation is payable without proof of fault by the sponsor or researchers; and ACC does not require the high level of proof of the causal link between trial product and personal injury that sponsors do under the current guidelines for compensation.

Recommendations

Patients who are participating, or considering participating, in existing trials conducted for the manufacturer's benefit should be informed that they are explicitly excluded from ACC coverage. They should be told in plain language that if a serious injury or illness occurs during the trial, it may be extremely challenging to obtain any compensation or support from the sponsor; that there are few independent experienced resources available for affected trial participants; that expensive legal representation may be necessary; and that if compensation or support is forthcoming, it is likely to take considerable time for this to occur.

Table 2 shows that this information has not been stated on participant information sheets until recently. Even with the latest, most cautious information sheet provided by the ethics committees, it is doubtful that potential participants will truly understand the situation they may face if an injury occurs. Updated draft guidance for ethical committees in New Zealand is unchanged from previously,[4] even though cases such as this one have been discussed at the highest level within the ethics committees, the Ministry of Health and ACC,[5] so this situation is unlikely to change in the foreseeable future. There is a need for a political will to resolve this inequity for participants in trials conducted for manufacturers.

Given these concerns, people should consider very carefully whether they wish to participate in a trial being conducted for the manufacturer's benefit. Researchers and treating clinicians should also consider very carefully whether they wish to be involved with such trials, including inviting people to participate. The process for receiving support and compensation for a trial participant injured during a trial conducted for the benefit of a manufacturer is fraught with difficulties. At the simplest level, the current process seems unfairly stacked against the trial participant.

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Dr Bolland reports: I have no financial conflicts to declare. The views expressed in the article represent my own opinion: the manuscript has not been written on behalf of any of my employers, nor does it represent the views of any of my employers.

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Anti-NMDA receptor autoimmune encephalitis: a case report

Akram Shmendi, Stewart Shiu

A 42-year-old, previously healthy female presented to her local doctor with insomnia, difficulty concentrating and impaired short-term memory. She denied illicit drug use. Fluoxetine and temazepam were initiated for anxiety. However, she later developed confusion and paranoid delusions, with an impression that her partner was attempting to kill her.

On hospital assessment, the examiner noted mild confusion, inattention and impaired short-term memory. Physical examination was normal. Laboratory investigations including a chemistry panel, liver function, full blood count, thyroid function and urinalysis were all normal except for serum calcium of 3.0 mmol/L (adjusted for serum albumin) and elevated parathyroid hormone (PTH). HIV serology, syphilis screen and urine toxicology screen were all negative. Computed tomography (CT) of the head was normal.

Treatment for symptomatic hypercalcaemia was commenced in the emergency department. She became more agitated, with thoughts that the staff wanted to harm her. Intravenous aciclovir was empirically started for presumed encephalitis.

Lumbar puncture revealed clear cerebrospinal fluid (CSF) with 7 leukocytes/μL (with lymphocytic predominance) and 200 erythrocytes/μL. Protein and glucose were normal. A polymerase chain reaction (PCR) panel, gram stain and culture were all negative. CSF anti-N-methyl-D-aspartate (NMDA) receptor antibody test was positive. Magnetic resonance imaging of the brain was normal. CT of the chest, abdomen and pelvis, mammogram and breast ultrasound were negative for malignancy. Parathyroid hormone-related peptide (PTrP) was negative. Electroencephalogram was not performed.

Anti-NMDA receptor encephalitis was diagnosed. Aciclovir was stopped and intravenous immunoglobulin at 2g/kg/day for two days and 1g methylprednisolone daily for five days were administered, followed by oral prednisone 80mg daily. Psychiatry was consulted.

During her stay, she became mute and aggressive, with catatonic features and abnormal posturing. Transfer to the intensive care unit (ICU) was required for intubation and sedation. Rituximab and cyclophosphamide were added. On day 18 of admission, she was discharged from the ICU. The agitation resolved and her cognition showed gradual improvement.

She was discharged on day 51. Since discharge, she has continued to improve, managing independently but still with deficits in short-term memory and concentration. Six cycles of fortnightly cyclophosphamide were completed, and two further doses of rituximab are planned. Antipsychotic agents and psychiatrist follow-up continue for ongoing anxiety. Outpatient neck ultrasound and sestamibi parathyroid scan were consistent with a parathyroid adenoma, and parathyroidectomy is planned.

Discussion

Anti-NMDA receptor encephalitis is increasingly recognised, with over one hundred cases reported in the literature. Its true prevalence is unknown.[1] NMDA receptors are found in high density in the frontal-temporal and hippocampal regions,[2,3] playing a central role in modulating memory, cognition and learning.[4] This may explain the diversity of psychiatric symptoms seen in advanced stages, including decreased responsiveness, dystonia, dyskinesia, rigidity and opist-

hotonic postures.[5,6] Approximately 70% of patients have preceding prodromal symptoms including fever, headache and gastrointestinal or upper respiratory tract symptoms. [3,6] Anti-NMDA receptor encephalitis is associated with malignancy in up to 50% of patients, and over 90% of these are ovarian teratomas.[5]

Immunomodulation is the mainstay of therapy.[3] First-line immunotherapy consists of corticosteroids, intravenous immunoglobulin or plasmapheresis. Second-line therapy consists of rituximab or cyclophosphamide, or both.[3,5] Antipsychotics and benzodiazepines are used to treat psychosis and behavioural manifestations. Surgical resection of tumour in those with identifiable lesions often results in the rapid resolution of symptoms.[5]

Prognosis with treatment is generally good, with up to 75% of patients achieving full recovery or minimal residual deficits.[3] The remaining 25% of patients may experience severe disabilities, with mortality rates of 4–7%. Reported rates of relapse, which more often occurs in those without teratoma, range between 12% and 24%.[3]

Conclusion

Anti-NMDA receptor encephalitis is an increasingly recognised disease, and physicians should consider it in patients with acute confusion, lymphocyte-predominant CSF pleocytosis and negative investigations for infective pathogens. Early identification, immunotherapy and malignancy screening are the mainstays of management.

Competing interests:
Nil.

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Letter on an iceberg

Cheri Hotu, Sandra Hotu, Dawn Adair, Danny De Lore, Clarence Kerrison, George Laking, Myra Ruka, Kennedy Sarich, Jade Tamatea, Tane Taylor, Matthew Wheeler

"Cultural safety... involves doctors reflecting on their own views and biases and how these could affect their decision-making and health outcomes for the patient."[1]

We write as the Māori Health Committee of the Royal Australasian College of Physicians (RACP), a collective of Māori physician and paediatrician Fellows and trainees.

In the public sphere, issues are like icebergs. This somewhat hackneyed metaphor illustrates that, while one facet of an issue is perceived, what is not seen is the hidden substructure of power and culture that form and reinforce it, buoying the issue to prominence above the surface.

An iceberg recently appeared in the media. An article detailed comments made by a urologist at a scientific meeting in Queenstown in November 2020.[2] Later, the same urologist spoke at length regarding their journey towards an awareness of why their actions were offensive and racist.[3]

The urologist's actions recall the iceberg metaphor because what was said on the surface, its impact and its response failed to centre on the less-visible structures and systems of power and privilege that sustain those actions. These instances of racism are frequently excused as isolated, individual instances of ignorance. Meanwhile, the underlying structures and systems that enable this entrenched contempt towards tangata whenua to occur, without conscience or consequence, are perpetuated.

In a room of two hundred people, who collectively amass hundreds of years of study, research and training, a callous disregard for Māori experience was displayed. The audience heard the blinkered tolerance of a system that disenfranchises and denies Māori access to quality healthcare and blames them when they die, on average, seven years younger than non-Māori. That same system permitted inequity to be debated without Māori agency or inclusion in the discussion.

Those seemingly innocuous remarks said on the fly to garner some sort of locker-room camaraderie in fact spoke of the collective experience of racism for Māori in Aotearoa. A Māori attendee who made a formal complaint stood for all Māori, who tautoko his assertion of racism because they live with it as well. The health system is often dangerous for our people; they are disbelieved, belittled and their truth is undermined.

Te Kaunihera Rata o Aotearoa, the Medical Council of New Zealand, refreshed its standards for medical practitioners on cultural safety in 2019[1]. In addition to the cultural safety standards, the council published a peer standard, He Ara Hauora Māori, A Pathway to Māori Health Equity.[4]

> *"When considering the needs of your patients cultural safety requires you to reflect on, take ownership of, and consider in your practice ... challenging the cultural bias of individual colleagues or systemic bias within health care services, which may contribute to poor health outcomes for patients of different cultures."*[1]

Building cultural safety into clinical practice can be uncomfortable and confronting as it involves reflecting on one's own personal biases, power and privilege, and at times having to challenge our colleagues and the structures which shape our clinical practice. Culturally safe health practice in Aotearoa requires specific training and a Te Tiriti-principled framework for assessment and review.

It is the responsibility of organisations working within the health sector to instate explicit pro-equity and anti-racism policies. We advocate for medical professionals to educate themselves and begin ongoing, reflective practice. We urge all those working within the health sector to take action and to challenge the prevailing substructure of power and culture that exists beneath the surface.

Competing interests:
Dr Kerrison, Dr Laking and Dr Ruka are members of Hei Āhuru Mōwai, Māori Cancer Leadership Aotearoa.

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A Case of Congenital Absence of Pericardium and Left Half of Diaphragm

1921

While diaphragmatic hernia of traumatic origin is comparatively common, especially since the war, hernia resultingfrom congenital defects in the diaphragm is only rarely recorded. The present case is remarkable for the apparently complete absence of the left half of the diaphragm. Tjhere was no hernial sac and the abdominal viscera passed freely up into the thorax. A still more interesting feature is that at the operation the heard could be clearly seen through the abdominal incision uncovered by pericardium, and appearing under the costal margin. The history is as follows:—

Thomas G., aged 54, cabdriver, was admitted to the Christchurch Hospital under my care on 2nd February, 1921. He complained of chronic headache, giddiness, occasional vomiting, and feeling generally out of sorts. He said that all his life he had never been able to follow any strenuous occupation, though he had never noticed anything particularly wrong with himself until the present time. Ten years ago he had been kicked in the abdomen by a horse, and two years ago he had been operated on for acute appendicitis. His present trouble commenced indefinitely a few months ago, but the vomiting dated apparently from the time he received the kick from the horse. He is a man of medium build, spare and of rather poor physique. On examination, his heart was found to be displaced so far to the right that the apex could be seen and felt pulsating in the epigastric angle under the xiphisternum. The rhythm and sounds of the heart were normal. Both brachial arteries were tortuous, and the left radial pulse was almost obliterated. The systolic pressure in the right arm was almost 185m.m. The left side of the chest moved less well than the right; tactile fremitus was absent in the axilla and diminished in front and behind. The area of normal lung resonance and breath sounds on the left side varied from day to clay, depending as it did on the degree of flatulence present. On an average it reached down to the fifth rib in front and the seventh rib behind, while laterally it was seldom obtainable. Below this lung are there was tympanitic resonance which could be elicited high up in the axilla. Over the tympanitic area breath and voice sounds were absent. The right lung was hypertrophied, and the breath sounds over it were loud and harsh. A marked gastric succussion splash could he obtained.

We considered the possibility of pneumothorax, but X-ray examination put this out. Dr. W. Bates, radiologist to the hospital, reported that the bismuth meal revealed a very large stomach rising high into the chest and lying against the heart, the fundus filled with gas and evidently pushing the heart over to the right. No diaphragm could be seen on the left; on the right it was placed rather lower than normal, owing to the hypertrophy of the right lung. The stomach had passed so high up into the chest that the pylorus lay at its lowest point, and the duodenum seemed to have lost its loop and to have been pulled out straight by the upward drag of the stomach. The bismuth rapidly entered the small intestine. When the bismuth reached the large intestine the transverse colon could be seen passing obliquely up from right to left to the splenic flexure which lay above and behind the stomach at the level, in front, of the third intercostal space.

We made the diagnosis of diaphragmatic hernia, caused, perhaps, by the kick from the horse ten years previously, but we were puzzled to know why we could not see any diaphragm on the left side. An

extra degree of flatulence began to cause the man syncopal attacks—a new feature and largely of nervous origin, as he was very apprehensive of his condition. He was in so miserable a state that it was decided to attempt to reduce the hernia by operation, though the prospects of success were recognised to be rather poor.

Dr. A. C. Sandston operated. A vertical incision was made through the left rectus from costal margin to umbilicus and continued along the costal margin to the xiphisternum. On opening the abdomen no great omentum could be seen, and its lower edge was found appearing under the costal margin. The stomach passed high up out of sight into the thorax. Traction on it brought it down a few inches, but on being released it immediately returned. The transverse colon passed obliquely up towards the splenic flexure, which lay far out of sight behind the stomach and high up in the chest. Like the stomach, it could not be drawn down permanently. The left lobe of the liver reached only to the midline. No trace of diaphragm on the left could be made out. The most remarkable feature of all was the condition of the heart, which could be clearly seen and felt, lying free in the abdomino-thoracic cavity, naked of pericardium, its apex lying in the middle line of the body, under the xiphisternum. A hard white glistening cartilaginous substance covered the apex and lower two inches of the left ventricle behind, and in the region of the right auriculo-ventricular groove were three small fleshy cyst-like bodies, growing on the heart.

A second incision was made over the sixth rib in the posterior axillary line and a piece of this rib was removed. The surgeon passed his hand up through the abdominal incision to the rib incision, and nothing intervened but a thin membrane of parietal pleura.

Since there was no diaphragm on the left and no hernial orifice and no sac, there could be no hernia, and therefore the stomach and colon could not be restored to their normal position. Nothing could be done, and the incisions were therefore sutured and the man taken back to bed. For the following few days he was very blue and dyspnœic from bronchitis, but this passed off and he. returned to his former condition, though with his nervous system rather upset. At the present time, a month later, he is short of breath on exertion, and suffers some pains in his scars. His condition is otherwise unchanged. He certainly has a functioning left lung, since faint breath sounds can usually be heard in the left axilla and normal breath sounds can always be heard in front and behind in the upper part of the left chest, which moves fairly well. The lung, therefore, manages to fill and empty in spite of the apparent absence of the diaphragm, and in spite of the stomach and colon, which must lie against the lung and press on it. The condition is certainly a congenital one. Absence of the left half of the diaphragm as a congenital anomaly is referred to in Cunningham's Anatomy and in Choyce's Surgery, and cases are recorded in the proceedings of the Anatomical Society of Great Britain, June, 1900, and in the Journal or Anatomy and Physilogy (Vol. 34). Professor Keith, in his description of the development of the diaphragm, states that the commonest defect is a persistent dorsal pleuroperitoneal opening on the left side, which may occupy two-thirds of the left half of the muscle.

Absence of the pericardium is a much rarer condition, and I have so far been unable to find any reference to its occurrence, though no doubt previous cases have been recorded; there are few structures of the body which are not prone to congenital defects. The cartilage on the apex of the heart in the present case is probably a developmental remnant of the central tendon of the diaphragm. It will be remembered that the pericardium opposite the apex is normally attached to the central tendon. The fleshy cysts on the right auriculo-ventricular groove are, perhaps, similar remnants of the undeveloped muscular portion of the diaphragm. Absence of the pericardium raises the interesting question of the function of that structure. Evidently, as in this case, it is not an essential part of the human anatomy.

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Incidence, pathological spectrum, and long-term outcomes of adult glomerulonephritides in the Midland Region Renal Centre between 2010 and 2019

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INTRODUCTION: Glomerulonephritis (GN) is the second leading cause of chronic kidney disease and has a major health implications globally.[1] Glomerulonephritis can often results in end stage kidney disease (ESKD) and is associated with significant morbidity and mortality. There is wide geographical variation globally in term of the epidemiological data of kidney disease. There is currently a lack of information on the epidemiology of biopsy-proven kidney disease in New Zealand, partly due to the unavailability of a national kidney biopsy registry. Furthermore, there is no data on clinical outcomes relating to disease groups, making prognostication in New Zealand difficult. To investigate this, we conducted a retrospective cohort study of all adult kidney biopsy performed between 2010–2019 involving five district health boards (Waikato, Bay of Plenty, Lakes, Tairāwhiti and Taranaki) in Midland Regional Renal Centre (MRRC).

AIMS: To understand the distribution of GN diseases in MRRC population. To describe the patient demographics in which biopsy-proven GN are completed. To match the GN with the most common clinical presentations. To investigate the clinically significant outcomes of specific GN. To evaluate ethnic discrepancies and outcomes of those with biopsy-proven GN.

METHODS: The keyword 'Renal Histo' was used to complete a retrospective search in the Waikato Hospital enterprise software for histopathology reports of all patients over 15 years of age between 1 July 2010 and 30 June 2019. The following data points were collected: age, sex, prioritised level 1 ethnic codes, primary histology diagnoses, date of death, clinical presentation and type of renal replacement therapy (ie, dialysis status or transplantation). Microsoft Excel 2016 and the in-built Visual Basic Applications were used for data collection and preparation. RStudio v1.2 was used for statistical analysis and data visualisation. Non-glomerular renal biopsy diagnoses (including kidney transplantation, kidney malignancy, hypertensive nephrosclerosis, or tubulointerstitial diseases, inconclusive diagnosis, suboptimal biopsies, or biopsy showing normal kidneys) were included in the biopsy rate calculations but excluded from the GN-specific analyses. Chi-square analysis for categorical data was used to assess statistical significance. Population data was acquired using the Census for the Midland region for each district health board from 2010 to 2019.

RESULTS: A total of 1,360 adult kidney biopsy reports were extracted; of these, only 699 histopathology reports met the inclusion criteria. The renal biopsy crude incidence in the Midland region through this time is 15.88 php/yr (per hundred thousand people per year) with GN identified at a rate of 8.16 php/yr. The average age of biopsy in adults was 53.4 years which is higher than when compared with other nations[2] (United Kingdom at 49 years old; Poland at 40.5 years old). The crude incidence increased with age (15–34 years old at 5.59 php/yr; 34–49 years old at 8.89 php/yr; 50–64 years old at 12.20 php/yr; and ages 65 and above at 12.91 php/yr). 55% of biopsies were performed on males (crude incidence of 4.45 php/yr) while 45% were completed on females (crude incidence of 3.70 php/yr). The incidence of biopsy-proven GN has increased over the last decade with the highest year in 2019 at 10.56 php/yr. Overall, IgA nephropathy (IgAN) had the highest crude incidence overall at 1.20 php/yr, followed by focal segmental glomerulosclerosis (FSGS; 1.11 php/yr), and membranous glomerulonephritis (MGN; 0.78 php/yr). The most common clinical manifestations of biopsy-proven GN is persistent proteinuria (35.7%), followed by unexplained rapid renal deterioration (24.6%) and haematuria (18.6%); with nephrotic syndrome being the least common (16.6%). Most of the kidney biopsies in the last 10 years were completed on European patients (58.7%) followed by Māori patients (29.0%). However, once adjusted by respective ethnic popula-

tions the highest incidence of biopsy-proven GN was in the Pasifika population (13.98 php/yr), followed by the Māori population (12.92 php/yr), then the Asian population (12.90 php/yr) and finally European and patients who identified as other ethnicity at 8.07 php/yr. Renal replacement therapy as an outcome represented 11.3% of the patients who had biopsy-proven GN while 7.4% had a ONE-year post-biopsy all-cause mortality. There was no significance when comparing the various ethnic populations with the clinical outcomes of renal replacement therapy (p = 0.092) or all-cause mortality 1-year post-biopsy (p = 0.111).

CONCLUSION: This study provides an overview of the patient demographics and biopsy-proven GN distribution across the Midland region. The inclusion criteria of histology reports for this study only accepted those with a confirmed histopathology primary diagnosis and thus does not include those with only clinical signs without a renal biopsy. The Midland region has an older average age of biopsy than other countries but the disease distribution is comparable to other nations. When examined, ethnicity alone was unable to show a statistically significant difference in clinically significant outcomes. This research provides a foundation for a renal biopsy registry in the Midland region to enable recognition of patterns of glomerular disease which will improve patient care and allow prognostication.

Ethnicity, deprivation and access to endoscopic sinus surgery

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INTRODUCTION: Resource constraints limit the provision of care to patients with chronic rhinosinusitis (CRS) in New Zealand. CRS may be under-appreciated among Māori and Pacific people or those of lower socioeconomic status (SES) due to barriers in access to healthcare.

METHODS: A single surgeon retrospective study of all cases of comprehensive endoscopic sinus surgery (ESS) at Waikato Hospital between January 2017 and December 2019 was performed. The ethnic composition and deprivation status of study patients were compared to the Waikato District Health Board (WDHB) population. Access to ESS was measured by calculating the waiting time to first clinic appointment and surgery and distance travelled by patients to reach WDHB.

RESULTS: A total of 177 patients were included. Minority ethnic groups such as Māori, Pacific people and Asians were under-represented in sinonasal surgery whilst Europeans were over-represented (p=.002). More than the expected number of the most deprived and least deprived patients underwent ESS. Distance travelled to reach WDHB did not differ significantly across ethnicities (p=.09), or deprivation scores (p=.64). Multiple regression model found that ethnicity, deprivation score and distance from hospital did not significantly affect the waiting time for clinic or surgery for patients (p =.55, p=.27).

CONCLUSIONS: This is the first study to describe the demographics of patients undergoing ESS in New Zealand. Our results highlight inequities with particular respect to ethnicity. This encourages all clinicians to customize their care in order to address these inequities.

Cardiac electrophysiology procedures at Waikato Hospital: four years of practice

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BACKGROUND: Waikato Hospital is the tertiary referral centre for invasive electrophysiology (EP) for 1,027,780 people in the five Midland district health boards.

AIMS: We describe the amount and type of work performed from 2017 to 2020, including procedural complications and success rates.

METHODS: Data recorded on the day of procedure was reviewed. Intra-procedural success as judged by the operator was recorded at the time of operation. Complications on the day of the procedure were available for all patients. Medical records were reviewed via electronic medical record to capture complications at 30 days.

RESULTS: Procedures were performed in 1,223, comprising of 787 (64.3%) males, mean age 59.2±14.8y. Indications for ablations were flutter alone in 329 (26.9%), atrioventricular nodal re-entry in 133 (10.9%), accessory pathway in 72 (5.9%), atrial fibrillation ± flutter in 422 (34.5%), atrial tachycardia in 37 (3.0%) and ventricular arrhythmia in 104 (8.5%), with 126 (10.3%) EP studies without ablation. Complications occurred in 84 (6.9%) patients. These comprised of 51 (4.2%) minor complications and 33 (2.7%) major complications. Ablation for ventricular tachycardia appears to carry the most risk, with a complication rate of 14.4% (5.8% being major complications). Overall, 88.6% were deemed successful as judged by the operator at the time of the operation. Of the major complications, there were eight tamponades (one requiring open surgery, all others drained percutaneously), seven strokes/TIA, 6 atrioventricular blocks, three major haemorrhages, two phrenic nerve injuries, two vascular injuries, two pericarditis with effusions, one bacterial endocarditis and one pulmonary

embolism. One patient died due to cardiogenic shock during a procedure for ventricular tachycardia without ablation occurring.

CONCLUSIONS: The case mix of EP procedures at Waikato Hospital is diverse with day of procedure success and complication rates varying according to ablation indication. Ablation for atrial tachycardia appears to be the least successful procedure with a success rate of 70.3%; however, this procedure only represents 3% of the caseload.

Features of the gut microbiome in patients with acute coronary syndrome

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BACKGROUND: Bacterial populations within the body may promote atherosclerotic cardiac disease and thereby conditions like the acute coronary syndromes (ACSs). To explore this in a New Zealand patient population, we studied the gut bacterial microbiome in ACS patients and also measured their blood markers of inflammation and gut integrity.

METHODS: Male ACS patients (n=25) were recruited at the Cardiac Care Unit (Waikato Hospital, New Zealand) and stool and plasma samples were collected. The control group (n=13) were healthy age- and gender-matched volunteers. Characterisation of the participant gut microbiomes was carried out using DNA sequencing of a bar-coding bacterial gene called 16S rDNA. Inflammation was assessed using plasma levels of C-reactive protein CRP, Interleukin-6, Transforming Growth Factor-β and Interleukin-10. Gut epithelial integrity was measured by quantifying the level of bacterial D-lactate and lipopolysaccharide (LPS) in the blood plasma.

RESULTS: Bacterial diversity was not significantly different between ACS and healthy controls. However, the ACS patient group had a significantly reduced abundance of the butyrate-producing genera Lachnospiraceae (p=0.001). C-reactive protein was significantly elevated in the ACS group (1.74 ± 0.37 vs 9.65 ±1.55 mg/l ± SEM; p<0.01), although the median level was below a clinically significant range. The other inflammatory markers were not different between groups. Interestingly, D-lactate was significantly elevated in the ACS group (0.092 ±0.005 vs 0.138 ±0.006 mM ±SD; p<0.001), indicating that the ACS group may have diminished gut integrity compared to the control group (however, LPS level was not different between the groups).

CONCLUSION: The results support efforts to further evaluate D-lactate as a marker in some cardiac patients, and to explore ways in which the abundance of the bacterial genus Lachnospiraceae in the gut could be improved to possibly promote a healthier, less atherogenic gut.

Psoriasis and depression

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BACKGROUND: Psoriasis is a chronic inflammatory skin condition associated with multiple co-morbidities such as psoriatic arthritis, metabolic syndrome, diabetes and hypertension. Chronic health conditions and psychiatric morbidity are strongly linked, but New Zealand data regarding psoriasis and depression are limited.

AIM: The study aimed to identify the prevalence of depressive symptoms among adult patients with psoriasis and identify risk factors that may link psoriasis to mental illness.

METHODS: We conducted a cross-sectional study during November–December 2020 at Waikato Hospital. One hundred adult patients with psoriasis completed the Patient Health Questionnaire (PHQ-9) and the Dermatology Life Quality Index (DLQI).

RESULTS: Depressive symptomology was observed in 25 patients (25% overall; 10% men; 15% women) with psoriasis. Symptoms of depression (PHQ≥10) were observed in patients with pre-existing depression (OR=9.86 p<0.0001) or anxiety (OR=4.57 p=0.007), psoriatic arthritis (OR=3.03 p=0.042), and high DLQI scores (OR=1.146; p=0.0002). Analysis using univariate linear regression predicted that in addition to a past medical history of psoriatic arthritis, depression, and anxiety; age, genital involvement, alcohol use and morbid obesity are significant factors that affect the PHQ-9 score.

CONCLUSION: Our results are consistent with previous research, which suggests that there is a high prevalence of depression, and patients experiencing distress should be screened and further referred.

PASI vs PO-PASI: a comparison of Patient-Oriented PASI (PO-PASI) with clinician score PASI

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BACKGROUND: We assessed the validity of the Patient-Oriented Psoriasis Area and Severity Index (PO-PASI) tool by comparing it to the widely used and validated physician-oriented tool Psoriasis Area and Severity Index (PASI).

METHODS: The study conducted at the Dermatology Department of Waikato Hospital in Hamilton, New Zealand, enrolled one hundred patients

(100) with physician-diagnosed psoriasis aged ≥18 over six weeks from November to December 2020. PASI and PO-PASI scores were recorded and compared for each participant.

RESULTS: We included the PASI and PO-PASI scores of 97 patients (49 male and 48 female; mean age: 49.07 years ± 14.54; mean duration of psoriasis: 21.25 ±14.7 years). Pearson correlation and ICC scores were as follows: Rho=0.866 (p-valu =0.0001) and ICC(3,1)=0.864 [95% confidence interval (0.803<ICC<0.907).

CONCLUSIONS: Our Pearson's r shows strong positive linear correlations amongst PASI and PO-PASI scores. This data translate into patient self-scores positively relating to physicians' PASI. Our results are in keeping with the literature on self-administered PASI-like tools, which actively demonstrates a moderate-to-strong correlation between patient-administered and physician-administered tools. Furthermore, our ICC scores suggest that we can be 95% confident that the PO-PASI score has interrater reliability of 'good' to 'excellent' compared to the PASI score. Our data actively demonstrates that the PO-PASI tool provides patients and physicians with a reliable scoring tool for remote use.

Surfactant Protein A in middle ear

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INTRODUCTION: Our laboratory has identified Surfactant Protein A (SPA) in the mouse middle ear. SPA is a component of surfactant fluid in the lower respiratory tract where it has a dual role of preventing collapse of lung alveoli as well as an antimicrobial action. Within the middle ear SPA may have a similar dual role insofar as the eardrum of the middle ear is also prone to collapse when negative pressure develops within the middle ear space. We have identified SPA within the epithelium of the mouse middle ear. We also confirmed its presence in mouse and rat lung where it is produced by type 2 alveolocytes.

MATERIALS AND METHODS: Using two mouse strains (BALBc and C57/B6), we used polyclonal antibodies to identify SPA within middle ear epithelia using immunohistochemistry (IHC). This finding was confirmed using western blot gel electrophoresis. We also used antibodies to cytokeratins (CK) which can distinguish type 2 alveolocytes (CK8/CK18 positive) from type 1 cells which exchange gas (CK7/CK19 positive). This approach helps to distinguish SPA-producing type 2 cells from type 1 which are SPA negative.

RESULTS: SPA was found to be present in some non-ciliated cells of the mouse middle ear. As control tissue, we also found that SPA was present in mouse and rat lung. The middle ear SPA was further confirmed by western blotting with positive controls from lung tissue. A further IHC finding was the presence of SPA in bone marrow nests adjacent to the middle ear cavity with direct communications to the middle ear. Bone marrow was also positive for CK 18 but not CK 19.

CONCLUSION: The presence of SPA positive cells within the mouse middle ear strengthens the concept of the middle ear as a derivative of the primitive respiratory tract. SPA positive cells may have an important role in both innate and acquired immunity in both acute and chronic otitis media respectively. They may act as progenitor cells and provide a constant source of renewed epithelium for the middle ear as well as contributing cellular debris towards the formation of biofilms.

The impact of COVID-19 pandemic restrictions on the cardio-respiratory health of New Zealanders

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CONTRIBUTORS: CLC, ES and RJH conceptualised the study. CM provided insight and data on virology trends. All authors contributed to the final study design. The analyses were done by SMF. SMF wrote the first draft of the manuscript with input from all authors. All authors critically revised the manuscript and approved the submitted version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

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SUMMARY: COVID-19 pandemic restrictions provided an opportunity to determine the impact these measures had on hospital admissions. There was a reduction in infectious respiratory admissions but not in non-infectious respiratory and cardiac admissions suggesting circulating respiratory viruses play a central role driving winter peaks in respiratory admissions but not heart failure.

BACKGROUND AND AIM: The COVID-19 pandemic has caused disruption to health, social interaction, travel and economies worldwide. In New Zealand, the Government closed the border to non-residents and required all arrivals to quarantine for 14 days. They also implemented a strict contact-restriction system to eliminate COVID-19 from the community. These measures also reduced the circulation of other respiratory viruses such as influenza and respiratory syncytial virus. We assessed the impact of these measures on hospital admissions for respiratory and cardiac diseases.

METHODS: National data on hospital admissions for each week of 2020 were compared to admissions for the previous five years. Analyses were curtailed after week 33, when a COVID-19 outbreak in Auckland led to different levels of pandemic restrictions making national data difficult to interpret.

RESULTS: The numbers of acute infectious respiratory admissions were similar to previous years before the introduction of COVID-19 restrictions, but then fell lower and remained low after the pandemic restrictions were eased. The usual winter peak in respiratory admissions was not seen in 2020. Other than small reductions during the period of the strictest contact restrictions, non-infectious respiratory and cardiac admissions were similar to previous years and the usual winter peak in heart failure admissions was observed.

CONCLUSIONS: The observed patterns of hospital admissions in 2020 are compatible with the hypothesis that circulating respiratory viruses drive the normal seasonal trends in respiratory admissions. By contrast, these findings suggest that respiratory viruses do not drive the winter peak in heart failure.

The impact of COVID-19 on eating disorder referrals and admissoins

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AIM: Overseas studies have reported increased eating disorder service needs during the COVID-19 pandemic, particularly in adolescents. Within New Zealand, anecdotal and media reports suggest similar changes, but are limited in scope and detail. We assessed demand for inpatient and outpatient eating disorder services at Waikato District Health Board (DHB) related to the COVID-19 pandemic.

METHODS: We undertook a retrospective analysis of clinical records for eating disorder admissions and referrals during 2019 and 2020 at Waikato DHB. Data on rates of admission, previous admissions, rates of referrals and referral acuity were collected for both children (<18 years) and adults (> 18 years). The relationship with COVID-19 was assessed by comparing data before and after lockdown in March 2020.

RESULTS: 106 admissions met inclusion criteria (n = 37 in 2019; 69 in 2020). Inpatient admissions for eating disorders increased markedly following lockdown (RR = 1.7, p=0.01), largely due to increases in the adult population (RR 2.0, p=0.005). The proportion of 'new patient' admissions for both age groups showed comparable increases (child RR =2.0, p=0.02; adult RR=2.3, p=0.03). Following lockdown, outpatient referrals increased in acuity (RR= 1.8, p=0.047) and volume (RR = 1.6, p=0.076) for children (<18 years) but not for adults.

CONCLUSIONS: This audit confirms a pandemic-related increase in demand for eating disorder services at Waikato DHB, with contrasting increases in admissions for adults and outpatient referrals for children. These increases have exacerbated resource constraints for already stretched services and compromised the provision of timely care. These findings are consistent with those reported overseas but should be interpreted with caution in light of our study's retrospective design and limited sample size.

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