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Corrigendum
World Thrombosis Day and prevention of hospital-associated venous thromboembolism

October 13 is World Thrombosis Day (WTD) (worldthrombosisday.org), the day chosen by the International Society on Thrombosis and Haemostasis (ISTH) to mark the culmination of its ongoing global campaign to develop awareness and improve care of thrombosis, the cause of one in four deaths worldwide. Thrombosis is an often overlooked and misunderstood condition, and what makes WTD important is that it engages not only healthcare professionals and policymakers but also the general public and patients. In particular, WTD concentrates on increasing awareness and improving care of venous thromboembolism (VTE) which is a particularly neglected area. October 13 seemed a fitting date for WTD as it is the birthday of Rudolf Virchow, the German pathologist who postulated that changes in blood flow, blood constituents or vessel damage predispose to VTE. Since its launch in 2014, WTD has grown exponentially. It now has over 1500 global partners in over 100 countries. In 2018, partners hosted over 10 000 events to raise the awareness of thrombosis as a global health problem, events that created 2.6 billion impressions and 96 million twitter chat impressions.

Knowledge is key to disease prevention, and public awareness of VTE is low. A global survey1 showed that while over 80% of the general public were aware of conditions such as hypertension, breast and prostate cancer and AIDS, awareness about deep vein thrombosis (DVT) and pulmonary embolism was lower, 44 and 54% respectively. Only 45% of people surveyed were aware that the majority of cases of VTE are preventable with even smaller numbers of people aware that hospital admission for surgical and medical treatment is a major risk factor for VTE. Awareness varied between countries, for example awareness about DVT being highest in the UK and Australia (86 and 80% respectively) and lowest in Japan and the Netherlands (13 and 20% respectively), highlighting the need for greater public awareness of this important global health issue.

As in previous years, the major focus for the 2019 WTD campaign will be the risk of hospital-associated VTE (HA-VTE) – VTE that occurs during admission and for up to 90 days post discharge. One in 1000 people worldwide will have a VTE every year and without the use of thromboprophylaxis up to 60% would be due to HA-VTE. Indeed, HA-VTE is the number one patient safety issue. In a study sponsored by the World Health Organization (WHO), VTE accounted for more deaths and disability-adjusted live years in low- and middle-income countries than any other hospital-associated events including nosocomial pneumonia, catheter-related bloodstream infections and drug errors, with an estimated incidence of 10 million cases annually.3

HA-VTE is preventable with the use of thromboprophylaxis but is poorly delivered globally. In 2010, in an effort to overcome poor delivery of thromboprophylaxis, NHS England mandated VTE risk assessment and appropriate use of thromboprophylaxis, in all English hospitals. Hospitals had to develop an infrastructure to support delivery but the effort has paid off. Since its implementation, there has been a 15.3% reduction in deaths due to VTE in the 90 days after hospital admission, from 72.1 per 1 001 000 in 2007/08 to 61.0 per 100 000 in 2017/2018.4

Looking at Australia and New Zealand, a population-based cohort study of HA-VTE in 1 865 059 patients admitted for greater than 48 h to acute hospitals in New South Wales between 2010 and 2013 showed an incidence rate was 9.7 per 1000 admissions. The majority of HA-VTE (71%) were diagnosed post discharge with a mortality rate of 4.3%, that was higher for events diagnosed in-hospital compared to post discharge (8.4 vs 2.6%, *P* < 0.001). Medical patients developed fewer HA-VTE than surgical patients (IRR = 0.60, 95% confidence interval (CI): 0.58–0.63) and were more likely to be diagnosed post discharge (OR = 2.19; 95% CI: 2.00–2.40).5 Further analysis showed marked variation in the incidence of HA-VTE that could only partly be explained by patient and admission characteristics and suggests possible differences in approaches to risk assessment implementation and thromboprophylaxis.6

In 2009, the Australian National Health and Medical Research Council published guidelines recommending but not mandating thromboprophylaxis for patients admitted to hospital for a broad range of medical, surgical and obstetric care.7 In 2018, the Australian Commission on Safety and Quality in Health Care published clinical care standards providing clearer recommendations that VTE risk assessment should be carried out in all patients admitted to hospital within 24 h of admission and repeated regularly.8 In 2014, the New South Wales
Government went further and published a policy directive making it mandatory that VTE risk assessment and appropriate thromboprophylaxis is carried out for all adult patients admitted to NSW public hospitals. Importantly, compliance with the directive is a condition for funding.

In New Zealand, the Health Quality and Safety Commission similarly recognises that prevention of HA-VTE is a major opportunity to improve patient safety. Each District Health Board responsible for public hospitals nationwide has been instructed to implement sustainable systems to support routine VTE risk assessment and thromboprophylaxis in adult hospitalised patients.

Patients and their families have a right to expect that they will be kept safe during their hospital stay and that all steps are taken to identify if they are at increased risk of preventable complications such as HA-VTE. Ideally, universal adoption of routine VTE risk assessment in all hospitalised patients should be offered in every hospital in every part of the world. Such a systematic approach to thromboprophylaxis would contribute greatly to the WHO’s plan of reducing premature mortality from non-communicable disease by 25% by 2025. Currently, there is no global approach proposed by the WHO to help reduce HA-VTE, but the ISTH is working closely with WHO’s patient safety group to meet this challenge. WTD provides an opportunity to focus ongoing attention to this preventable global health issue.

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References


Behaviour change techniques to optimise participation in physical activity or exercise in adolescents and young adults with chronic cardiorespiratory conditions: a systematic review

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Key words
behaviour change technique, chronic cardiorespiratory condition, physical activity, exercise, adolescent, adult.

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Abstract
Participation in regular physical activity decreases the risk of developing cardiometabolic disease. However, the proportion of people who participate in the recommended amount of physical activity is low, with common barriers including competing interests and inclement weather. In people with chronic cardiorespiratory conditions, participation in physical activity is reduced further by disease-specific barriers, time burden of treatment and unpleasant symptoms during physical activity. Addressing these barriers during adolescence and early adulthood may promote greater physical activity participation into older age. The aim of this review was to classify interventions aimed at optimising participation in physical activity as ‘promising’ or ‘not promising’ in people aged 15–45 years with chronic cardiorespiratory conditions and categorise the behaviour change techniques (BCT) within these interventions. Nine databases and registries were searched (October 2017) for studies that reported objective measures of physical activity before and after an intervention period. Interventions were classified as ‘promising’ if a between-group difference in physical activity was demonstrated. Michie et al.'s (2013) v1 Taxonomy was used to unpack the BCT within interventions. Across the six included studies (n = 396 participants), 19 (20%) of 93 BCT were described. The interventions of three studies were classified as ‘promising’. The most commonly used BCT comprised goal setting, action planning and social support. Five BCT were solely used in ‘promising’ interventions. Our review demonstrated that only 20% of BCT have been utilised, and those BCT that were used only in ‘promising’ physical activity interventions in adolescents and adults with chronic cardiorespiratory conditions were isolated.

Introduction
Participation in physical activity, which may include engaging in structured exercise, is important for maintaining health and well-being in the general population.1 International societies recommend that adults participate in physical activity or aerobic exercise at a moderate intensity for at least 150 min per week or at a vigorous intensity for at least 75 min per week.1,2 Adolescents are recommended to participate in at least 60 min of moderate to vigorous physical activity per day.3 Despite the numerous physical and psychosocial health benefits of physical activity, as few as 50% of adults and 10% of young people appear to meet the current recommendations for sufficient participation in physical activity.1,4 The reasons for insufficient participation in physical activity in the general population include competing time interests,
attitudes and motivation and environmental factors, such as inclement weather.\(^5\)\(^-\)\(^9\)

In addition to the health benefits attained by the general population, for people with chronic cardiorespiratory conditions, participation in physical activity and exercise may optimise function, improve quality of life, slow the progression of disease and enhance prognosis.\(^10\)\(^-\)\(^16\) People with chronic cardiorespiratory conditions, however, participate in less physical activity than their healthy counterparts.\(^5\)\(^,\)\(^17\)-\(^20\) In addition to barriers experienced by the general population, people with a chronic cardiorespiratory condition are likely to face disease-specific barriers to participation in physical activity, such as the time burden of treatment\(^6\) and unpleasant symptoms of breathlessness, leg muscle and general fatigue during physical activity.\(^7\)\(^,\)\(^21\) Participation in physical activity is of particular concern during ‘transitional’ years, such as adolescence and early adulthood. During this developmental period, peer relationships, disease stigma and an increased level of autonomy become important influencing factors to treatment adherence.\(^22\)-\(^24\) The presence of data demonstrating a positive relationship between physical activity level in early life and physical activity levels later in life\(^5\)\(^-\)\(^27\) suggests that targeting physical activity and exercise behaviour in adolescents and young adults is likely to be important to create positive habits and assist this population throughout the ageing process.

To address issues related to poor participation in physical activity, there is growing interest in the use of behaviour change techniques (BCT), which are the active component(s) of an intervention aimed to modify existing or stimulate new behaviours.\(^28\)\(^,\)\(^29\) Michie et al.\(^29\) designed a universally applicable Taxonomy in which 93 individual BCT are clustered into 16 common groups. This Taxonomy has been applied to research that aims to reduce total sedentary time,\(^30\) facilitate smoking cessation\(^11\)\(^,\)\(^12\) and optimise diabetes care.\(^33\) Researchers have yet to apply the Taxonomy to understand the BCT used in physical activity interventions with adolescents and young adults with a chronic cardiorespiratory condition, a population who face internal (e.g. motivation and attitudes), external (e.g. competing time interests) and disease-specific barriers to physical activity and exercise.\(^5\)\(^,\)\(^6\) The aims of this review were, in adolescents and adults with one or more chronic cardiorespiratory conditions, to (i) classify interventions aimed at optimising participation in physical activity as either ‘promising’ or ‘not promising’ and (ii) to identify and categorise BCT described in interventions that have been classified as ‘promising’ and ‘not promising’.

### Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines\(^34\) and was prospectively registered with PROSPERO (CRD42017068892).

### Eligibility criteria

Studies were eligible for inclusion in this review if: (i) the mean age of the sample was between 15 and 45 years; (ii) all participants had a chronic cardiorespiratory condition, that could include but was not limited to asthma, cystic fibrosis (CF), interstitial lung disease, congenital heart disease or cardiovascular disease; (iii) the study design was multi-arm with at least one participant group exposed to an intervention that incorporated BCT included in the Taxonomy (i.e. experimental group)\(^29\) and one group acting as a control; and (iv) objective measures of physical activity were collected before and after the intervention period through either wearable technology (e.g. accelerometer, inclinometers, heart rate monitors, portable metabolic monitors or step count monitors) or direct observation.

Studies were excluded if they used a cross-over or single-group design or were published in a language other than English. Conference abstracts were excluded.

### Information sources and search

Studies were identified from computerised literature searches of PEDro (Physiotherapy Evidence Database), CENTRAL, MEDLINE, CINAHL, EMBASE (through OVID) and PsychINFO databases from their inception to October 2017. Clinical trial registries comprising ClinicalTrials.gov, the World Health Organisation trials portal and the Australia New Zealand Clinical Trials Registry were searched in October 2017 for protocols meeting the eligibility criteria. Where eligible protocols were identified, authors were contacted to determine if the study had been published. The search strategy used for MEDLINE can be found in Supporting Information Appendix S1. This search strategy was adapted for use in other databases.

### Study selection

Two review authors (A. S. and H. L.) used the Covidence\(^35\) software to screen independently titles, abstracts and full papers identified by the search process against eligibility criteria. Disagreement between the two authors was resolved by discussion.
Data collection process

A data extraction template was developed a priori. A single review author (A. S.) undertook data extraction, the results of which were confirmed by other review authors (H. L. and D. G.). Data were extracted from eligible studies in relation to the following components:

Study characteristics

Title, year, sponsorship, study design, number of participant groups, between-group differences at baseline and sample size.

Participant characteristics

Participant groups, average age, cardiorespiratory condition and eligibility criteria.

Intervention

Description (verbatim), number of interventions, monitoring and duration of sessions per week, intensity of physical activity/exercise prescribed, financial assistance received for study participation, additional support and setting.

Comparator

As per intervention.

Outcomes

Assessment time point, outcome measure, between-group differences.

BCT

Extraction of BCT from the interventions of included studies was conducted using Michie et al.’s v1 BCT Taxonomy. The Taxonomy comprises 16 major ‘groups’ of BCT: Goals and Planning, Feedback and Monitoring, Social Support, Shaping Knowledge, Natural Consequences, Comparison of Behaviour, Associations, Repetition and Substitution, Comparison of Outcomes, Reward and Threat, Regulation, Antecedents, Identity, Scheduled Consequences, Self-Belief and Covert Learning. Each of these groups incorporates several individual BCT. For example, Group 1 (Goals and Planning) encompasses nine individual BCT: goals setting (behaviour) (1.1), problem solving (1.2), goal setting (outcome) (1.3), action planning (1.4), review behaviour goals (1.5), discrepancy between current behaviour and goal (1.6), review outcome goals (1.7), behaviour contract (1.8) and commitment (1.9). Data were extracted following completion of the BCT v1 Taxonomy online training module (A. S.) and were reviewed for quality by another review author who is experienced in the use of this Taxonomy (D. G.). A comprehensive list of the BCT v1 Taxonomy groups can be found in the supplementary material of the original article.

Risk of bias

Risk of bias was assessed using Cochrane’s seven evidence-based domains table. This tool reports on the methodological issues related to risk of bias in the following domains: ‘random sequence generation’ and ‘allocation concealment’ (selection bias), ‘blinding of participants and personnel’ (performance bias), ‘blinding of outcome assessment’ (detection bias), ‘incomplete outcome data’ (attrition bias), ‘selective outcome reporting’ (reporting bias) and ‘other bias’. Studies were scored as being at a ‘high’, ‘unclear’ or ‘low’ risk of bias for each domain.

Data synthesis

Classification of interventions

Interventions were categorised as having a ‘promising’ or ‘not promising’ influence on the level of participation in physical activity in adolescents and adults with chronic cardiorespiratory conditions. Interventions were classified as ‘promising’ if, following the intervention period, there was a significant between-group increase in physical activity or exercise levels in favour of the experimental group. Interventions were classified as ‘not promising’ if, following the intervention period, no significant between-group differences were reported for physical activity or exercise levels.

Identification and categorisation of BCT

Specific components of each intervention were ‘coded’ as BCT if sufficient detail was provided to validate the presence of the particular BCT on a target behaviour(s) and population(s). The BCT was labelled with ‘+’ if the authors were confident ‘beyond reasonable doubt’ that the BCT was present. If the BCT appeared to be present ‘in all probability’ from intervention description, but there was insufficient detail, the BCT was coded as ‘+’. For example, in one study, ‘Patients in the intervention group were called several times during the first 6 months of the study to check on their activity behaviour and, if necessary, to offer additional help’ was coded as ‘social support (unspecified) with partial confidence (+)’ because there was insufficient detail pertaining to the content of the conversation of the phone support. All 93 individual BCT were considered for each of the interventions of the included studies. The BCT were summarised by number and type.

Results

The search of electronic databases yielded a total of 7692 records, of which 1116 were duplicates. The titles and
abstracts of remaining records (n = 6576) were screened against eligibility criteria. Following the removal of ineligible records (n = 6428), full texts of the remaining studies were screened for eligibility. The main reasons for exclusion following full-text review were related to no objective measure of physical activity (n = 29) and the mean age of participants >45 or <15 years (n = 104) (Fig. 1).

Characteristics of included studies
All six included studies were randomised controlled trials (RCT), conducted in Brazil,39 The Netherlands,40 Germany,38 Switzerland and Germany,41 Ireland42 or Australia.43 Across the included studies, there were 396 participants aged (mean ± standard deviation (SD)) 15 ± 3 years to 45 ± 12 years. Sample sizes ranged from 37 to 143 participants, with 183 (46%) being female. Studies included people with asthma (n = 2),39,43 CF (n = 2)38,41 and congenital heart disease (n = 2).40,42 Further study characteristics are presented in Appendix S2.

Risk of bias
The quality of included studies was poor to fair (Fig. 2). No two studies were identical in terms of the risk of bias assessment. Performance bias (blinding of participants and personnel) was high across all studies, and only one study was rated as having a low risk of detection bias (blinding of outcome assessor). Intention-to-treat analysis was reported in three studies.39,41,42 Three studies reported not reaching the required sample size.38,42,43 Further details on the risk of bias assessment can be found in Appendix S3.

Interventions
Intervention delivery was highly variable in terms of frequency and duration of contact, supervision provided, monitoring, intensity of the physical activity and/or exercise prescribed, support provided, location and length of the intervention period (Table 1). Five studies implemented exercise training programmes.38,40–43 In three of these studies,38,42,43 promotion of physical activity was added to the exercise training programme. One study focused on the promotion of physical activity without an exercise training component.39 The duration of interventions ranged from 10 weeks to 6 months. Interventions were supervised (n = 3),40,41,43 unsupervised (n = 1)39 or partially supervised (n = 2).38,42 In one of the partially supervised interventions,38 participants were asked to increase their participation in a sport of their choosing by 3 h each week. For example, some participants undertook resistance training in a fitness centre (supervised), other participants opted to complete independent endurance sports (cycling, jogging or swimming) and some chose to complete a mixture of these...
options. In the other partially supervised intervention, participants undertook group education sessions but were provided with an independent programme to complete at home to increase their activity.

Four of the six included studies had a two-arm design (i.e. intervention and control group). One study had a three-arm design (i.e. two intervention groups and a control group), and one study had a four-arm design (i.e. three intervention groups and a control group).

**Interventions considered promising versus not promising (aim 1)**

Of the six included studies, half (n = 3) were considered to have a ‘promising’ effect of physical activity or participation in exercise.

**BCT across all studies (aim 2)**

Of the 93 individual BCT outlined in the v1 Taxonomy, 19 (20%) were represented within the study interventions (Fig. 3). The number of individual BCT identified within each of the included studies ranged from 2 to 10, with (mean ± SD) 6 ± 3 BCT described per study. The most commonly used BCT across included studies were goal setting (behaviour) (indicated in Fig. 3 as 1.1) (5/6 studies) and action planning (indicated in Fig. 3 as 1.4) (5/6 studies). Eight BCT were coded only once across the six studies: problem solving (indicated in Fig. 3 as 1.2), goal setting (outcome) (indicated in Fig. 3 as 1.3), feedback on behaviour (indicated in Fig. 3 as 2.2), information about health consequences (indicated in Fig. 3 as 5.1), credible source (indicated in Fig. 3 as 9.1), pros and cons (indicated in Fig. 3 as 9.2), comparative imagining of future outcomes (indicated in Fig. 3 as 9.3) and adding objects to the environment (indicated in Fig. 3 as 12.5).

**BCT used in promising interventions**

The most frequently used BCT in interventions categorised as having a ‘promising’ effect on physical activity or participation in exercise were goal setting (behaviour) (indicated in Fig. 3 as 1.1) and action planning (indicated...
in Fig. 3 as 1.4). Each of these BCT were utilised on four occasions across three separate interventions.\textsuperscript{18,19,42} Five BCT were solely used in ‘promising’ interventions: problem solving (indicated in Fig. 3 as 1.2), information about antecedents (indicated in Fig. 3 as 4.2), information about health consequences (indicated in Fig. 3 as 5.1), pros and cons

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Coelho\textsuperscript{39}</th>
<th>Duppen\textsuperscript{40}</th>
<th>Hebestreit\textsuperscript{38}</th>
<th>Kriemler\textsuperscript{41}</th>
<th>Morrison\textsuperscript{42}</th>
<th>Scott\textsuperscript{43}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Asthma</td>
<td>Congenital heart disease</td>
<td>Cystic fibrosis</td>
<td>Cystic fibrosis</td>
<td>Congenital heart disease</td>
<td>Asthma</td>
</tr>
<tr>
<td>Description of intervention</td>
<td>All participants attended an individualised standardised education session</td>
<td>Intervention group: provided with an aerobic exercise training programme (aerobic dynamic cardiovascular training and a warm-up/cool-down)</td>
<td>Control group: instructed to continue their normal daily life</td>
<td>Control group: asked to maintain a constant physical activity level</td>
<td>Intervention group: invited to attend activity day, which included a motivational interviewing style group, pros and cons of exercise and visualisation techniques</td>
<td>Intervention group (1) (exercise intervention): provided with a gym membership and group personal training. The same gym was used by participants to ensure comparable programme. Designed by an exercise physiologist</td>
</tr>
<tr>
<td>Intervention group</td>
<td>received a dairy to register asthma exacerbations. Also provided with a step-based (walking) physical activity prescription plan with targets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention group (2): provided with a dietary intervention (&quot;control&quot;)</td>
</tr>
<tr>
<td>Control group</td>
<td>received a diary to register asthma exacerbations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention group (3): (combined group): completed exercise and diet intervention</td>
</tr>
<tr>
<td>Duration of the intervention period</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>6 months</td>
<td>6 months</td>
<td>6 months</td>
<td>10 weeks</td>
</tr>
<tr>
<td>Time</td>
<td>Both groups: 1-h standardised education sessions</td>
<td>Intervention group: three times per week for 1 h</td>
<td>Intervention group: three times per week for 30–45 min for the first 6 months of the study</td>
<td>Intervention group: provided with a diary to register exacerbations, received a dairy to continue their usual care, asked to maintain a constant physical activity level</td>
<td>Intervention group: An education session and follow-up letter summarising discussions. Monthly follow-up</td>
<td>Intervention group (1 and 3): 1-h personal training session, gym membership/programme and daily step goal</td>
</tr>
<tr>
<td></td>
<td>Intervention group: advised to increase physical activity to five times per week for &gt;30 min</td>
<td>Control group: no change</td>
<td>Control group: no change</td>
<td>Control group: no change</td>
<td>Control group: no change</td>
<td>Intervention group (2): (&quot;control&quot;) seven 1-h clinic visits and four 10-min phone calls with a dietician</td>
</tr>
<tr>
<td></td>
<td>Control group: advised to increase physical activity to five times per week for &gt;30 min</td>
<td></td>
<td>time commitment</td>
<td>time commitment</td>
<td>time commitment</td>
<td>Not specified</td>
</tr>
<tr>
<td>Intensity of intervention</td>
<td>Each participant asked to commence walking at a moderate intensity (talk test – explain this). Progressive step-based goals</td>
<td>Interventions:</td>
<td>Below gas exchange threshold (equivalent heart rate)</td>
<td>Strength training: set by fitness centre staff. Weight increase by 5% per week if the participant could do &gt;9 repetitions Anaerobic training: commenced at 65% VO\textsubscript{2peak}</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
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Table 1 Characteristics of interventions
(indicated in Fig. 3 as 9.2) and comparative imagining of future outcomes (indicated in Fig. 3 as 9.2). Of the 24 occasions on which BCT were used in ‘promising’ interventions, 22 were described in sufficient detail to validate their presence with complete confidence (++, ‘beyond reasonable doubt’)).

BCT used in not promising interventions

The most commonly coded BCT amongst interventions with a ‘not promising’ effect on physical activity or participation in exercise was goal setting (behaviour) (indicated in Fig. 3 as 1.1), which was identified and coded on four occasions by four interventions.41,43 On one of these occasions, the BCT could only be coded with partial confidence (+, ‘in all probability’).43 Goal setting (outcome) (indicated in Fig. 3 as 1.3), feedback on behaviour (indicated in Fig. 3 as 2.2), credible source (indicated in Fig. 3 as 9.1) and adding objects to the environment (indicated in Fig. 3 as 12.5) were used only in ‘not promising’ interventions. Of the 27 occasions BCT were used in ‘not promising’ interventions, 22 were described in sufficient detail to validate their presence with complete confidence (++, ‘beyond reasonable doubt’).
Discussion

This systematic review is the first to apply the BCT v1 Taxonomy\(^{29}\) to interventions aimed at optimising physical activity, which may have included participation in exercise, in adolescents and younger adults with chronic cardiopulmonary conditions. Six studies met our inclusion criteria and were of fair to poor quality. The three main findings of this systematic review were as follows: (i) only 20% of the individual BCT outlined in the v1 Taxonomy were represented within the interventions of included studies, (ii) three of the six studies had interventions that had a ‘promising’ influence on physical activity or participation in exercise and (iii) five BCTs (namely, *problem solving*, *information about antecedents*, *information about health consequences*, *pros and cons* and *comparative imagining of future outcomes*) were solely used in ‘promising’ interventions.

The finding that few (20%) of the BCT outlined in the v1 Taxonomy\(^{29}\) were represented within the interventions of included studies support earlier work that report a limited number of BCT in studies aiming to optimise physical activity or implement home-based cardiac rehabilitation in adults with chronic obstructive pulmonary disease (COPD)\(^{44}\) and cardiac disease\(^{45}\) respectively. A recent systematic review on the use of BCT by physiotherapists in interventions aimed at increasing physical activity has demonstrated that ‘promising’ interventions used more BCT than ‘not promising’ interventions.\(^{46}\) This finding contrasts with our work, which identified a comparable number of BCT between the interventions of ‘promising’ and ‘not promising’ studies. One possible reason for this disparity is that our study only includedRCT, and the decision to classify interventions as ‘promising’ was the finding of significant between-group differences in objective measures of physical activity. In

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**Figure 3** Behaviour change techniques (BCT) coded within the included studies. <++>, BCT coded once within the study; ++, BCT coded more than once within the study (the number in the box indicates number of occasions that the BCT was used). ‘++’ next to the author’s name indicates that intervention within the study was categorised as ‘promising’. A ‘++’ next to the BCT indicates that reviewers were confident beyond reasonable doubt that the technique was present. A ‘+++’ next to the BCT indicates that the technique was present ‘in all probability’; however, supporting information was lacking.
contrast, the earlier systematic review included studies that provided lower levels of evidence (i.e. uncontrolled single-group studies with subjectively reported measures of physical activity).

Commonly used BCT were similar between ‘promising’ and ‘not promising’ interventions and included goal setting (behaviour) and action planning. Goal setting (behaviour) is defined as ‘setting or agreeing on a goal defined in terms of the behaviour to be achieved, for example, agreeing on a weekly exercise target’. Action planning is similar except that, in addition to defining a goal, explicit instruction is given regarding the context, frequency, duration and/or intensity of the behaviour. Of note, action planning was used in all of the ‘promising’ studies and two of the three non-promising studies. Notwithstanding these similarities in BCT common to ‘promising’ and ‘not promising’ interventions, there were two noticeable differences in the way they were applied: (i) specificity of the goal (i.e. promotion of physical activity rather than just participation in the exercise program); and (ii) length of intervention; that is, compared to ‘not promising’ interventions, which tended to focus solely on an exercise programme, ‘promising’ interventions included the promotion of physical activity either alone or in combination with an exercise programme. For example, discussed ways to increase physical activity, and in the study by Hebestreit et al., physical activity counselling and discussion of an activity plan were undertaken. Our data suggest that, when attempting to increase participation in physical activity, it is the embedding of specific instructions regarding the execution of this health behaviour (i.e. action planning) within an exercise training intervention that is needed to optimise success. In addition, the current study demonstrated that longer interventions seem to be more advantageous than shorter interventions to change physical activity behaviour in adolescents and adults with a chronic cardiorespiratory condition; that is, the majority of ‘promising’ interventions were 6 months or longer in length, compared to an average of 12 weeks or less for the majority of ‘not promising’ interventions. This finding is in agreement with the results of a study of pulmonary rehabilitation in people with COPD which demonstrated that a 3-month intervention improved exercise capacity, muscle force and quality of life. However, physical activity only improved after 6 months of intervention. The reason that longer interventions appear to be advantageous compared to shorter interventions may be due to the time it takes to implement physical activity BCT and/or the time is takes for these BCT to influence positively the target behaviour.

Several BCT were described only within ‘promising’ interventions. Problem solving, which is categorised within the Goals and Planning group of the BCT Taxonomy, was especially solely used in ‘promising’ interventions and suggests that, when attempting to change physical activity, it is important to offer problem solving together with goal setting (behaviour) and action planning. Given the magnitude of barriers for people with chronic cardiorespiratory conditions, identifying obstacles and potential solutions in advance is important for ongoing adherence to physical activity and exercise programmes. Earlier work has also reported the value of highlighting behavioural ‘norms’ to participants, particularly in the context of goal setting, and this is likely to explain why information about antecedents and information about health consequences were identified within ‘promising’ interventions. Another BCT used only in ‘promising’ interventions was pros and cons, whereby ‘a person is advised to identify and compare reasons for wanting (pro) or not wanting (con) to change a behaviour’. This technique, commonly referred to in the literature as decisional balance, is an important element of behaviour adoption and positive decisional balance (i.e. higher perceived pros than cons) has been shown to influence strongly the participation in physical activity. In addition, positive decisional balance may have a role in long-term participation in physical activity in people who are already active. Finally, comparative imagining of future outcomes, or mental contrasting, was also used solely in ‘promising’ interventions. Similar to decisional balance, this technique emphasises the need for action upon a goal through the consideration of a positive future achievement of a behaviour (e.g. completing physical activity 30 min per day) with negative barriers (e.g. motivation, inclement weather, competing time interests) and is particularly useful in adolescents and adults. Our finding that these BCT were described in ‘promising’ interventions is supported by earlier work. For example, in a systematic review investigating the use of BCT in cardiac rehabilitation programmes, information about health consequences was only used by efficacious cardiac rehabilitation programmes. Likewise, in another review investigating BCT utilised by physiotherapists for physical activity interventions in people with non-communicable disease, problem solving and information about health consequences were only identified in interventions considered efficacious at improving physical activity.

Although this review used a comprehensive search strategy to find studies that met our eligibility criteria, the results should be interpreted with caution as the number of studies included was small, and their quality
was variable. Furthermore, on several occasions, we were unable to code potential BCT with any confidence due to insufficient details reported for the intervention. The breadth of uncoded BCT, techniques only coded on a single occasion, and the heterogeneity and limited number of included studies reduce our confidence in concluding which BCT are likely to be the most useful to optimise physical activity in adolescents and adults with chronic cardiorespiratory conditions. This uncertainty highlights the underdevelopment of the evidence base in this area. It is the authors’ hope that the use of the BCT v1 Taxonomy in this paper will prompt others to report the active components of an intervention with clarity and consistency to facilitate meaningful future research, as well as the translation of efficacious interventions into clinical practice. Moreover, studies were only included in the review if the measurement of physical activity was device-based or through direct observation. While device-based measures of physical activity are more robust than self-reported measures of physical activity, studies aiming to optimise physical activity are more robust than self-reported measures of physical activity. Studies aiming to optimise physical activity or participation in exercise that utilised subjective measures of physical activity may have included BCT that have not been used in the studies included in the current review.

Conclusion
A relatively small number of potential BCT was identified within interventions aiming to optimise physical activity in adolescents and adults with a chronic cardiorespiratory condition. Although there was some overlap in the BCT described within ‘promising’ and ‘not promising’ interventions, BCT, such as problem solving, information about antecedents, information about health consequences, pros and cons and comparative imagining of future outcomes, were only used in those studies that reported ‘promising’ interventions. Despite the growing consensus surrounding the importance of BCT to change health behaviours, this systematic review has demonstrated that details of specific interventional BCT may be underreported or that BCT may not be considered fully when devising an intervention in adolescents and adults with a chronic cardiorespiratory condition. Currently, there is limited evidence to support the use of individual BCT or specific combinations of BCT over others within interventions aiming to optimise physical activity in this population. However, the findings of the current review suggest that ‘promising’ interventions may have to incorporate a combination of exercise programmes and the specific promotion of physical activity and were offered over a duration of at least 6 months.

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Sawyer et al.


Supporting Information

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

Appendix S1. MEDLINE search strategy.
Appendix S2. Study characteristics.
Appendix S3. Evidence of risk of bias.
CLINICAL PERSPECTIVES

Secondary prevention of ischaemic stroke
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Key words
ischaemic stroke, secondary prevention, cryptogenic stroke, embolic stroke of unknown source, patent foramen ovale, left atrial appendage.

Abstract
Recent trials within the past few years have influenced not only how we treat patients immediately after acute ischaemic stroke, but also how we investigate for aetiology. With the advent of improved medications, procedures and monitoring devices, modern stroke prevention strategies are more individualised, but the decision-making process is more complex. We provide an approach to navigating these management options.

Introduction
Recent advances in stroke secondary prevention have complemented the hyperacute clot retrieval revolution. Consequently, the modern stroke physician is faced with several more decisions, the rationale for which will be highlighted in this perspective.

We will highlight facets of stroke secondary prevention subject to new evidence or availability in the Australian medical system. This includes dual antiplatelet therapy (DAPT), anticoagulation for embolic stroke of undetermined source (ESUS), prolonged cardiac monitoring with implantable loop recorders (ILR), percutaneous patent foramen ovale (PFO) occlusion and left atrial appendage (LAA) occlusion. There have been few practice-changing publications in the areas of management of blood pressure, lipids, blood glucose and lifestyle modifications and we have therefore not detailed these topics in this perspective article. A comprehensive review of most topics in stroke secondary prevention is available via the Stroke Foundation Clinical Guidelines for Stroke Management.1

Concepts in stroke prevention
Stroke secondary prevention options can be conceptually grouped into therapies that should be used unless there is a contraindication (e.g. lifestyle modification and antihypertensive medication) and treatments that first require a qualifying condition to be documented (e.g. anticoagulation for atrial fibrillation (AF)). The term cryptogenic unnecessarily conflates the two concepts of no cause being found and no specific therapy being needed; consider whether an ischaemic stroke associated with an ipsilateral carotid stenosis of almost 50% is truly ‘cryptogenic’. In addition, this term does not specify how extensive the work-up needs to be and it is therefore too non-specific to use to guide clinical practice.

To facilitate trials of direct oral anticoagulants (DOAC) the term ESUS was developed. This term requires specific investigations and results for a stroke to qualify for this label.2 In this scenario the stroke remains cryptogenic despite a specific, thorough but clinically practical work-up in the context of what was available at the time the DOAC ESUS trials were designed. However, ESUS was a research tool designed for a specific set of trials, and was not used to define the patient cohorts investigated in other contemporary trials assessing PFO closure or prolonged cardiac monitoring for AF, as discussed below. Therefore, these various approaches to stroke assessment have been investigated in non-overlapping patient groups and some patients were recruited into a
trial of one novel approach, while receiving another (e.g. in a Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and Safety of dabigatran versus aspirin in patients with ESUS, RE-SPECT ESUS, 6% of patients received an ILR"). Recruitment into future trials may be harmonised by starting with patients meeting the ESUS definition and adding other markers of risk.

Some secondary prevention management issues relate specifically to ‘young’ patients, including identifying and managing thrombophilias or PFOs. The risk of stroke increases exponentially with age, mostly linked to an atherosclerotic basis for these events. The corollary is that in younger patients, atherosclerotic mechanisms and treatments are less relevant and other factors such as PFOs are more relevant. Although a standardised definition for young stroke is lacking, across publications there has been a range of suggested cut-offs for young age, varying from 45–65. In this review we use ‘young’ to mean someone under 60 years of age with minimal atherosclerotic risk factors, to align with recent positive trials of PFO closure, while acknowledging our definition is not strict nor universally adopted.

It is worth noting that the data discussed in this review relate to stroke or transient ischaemic attack (TIA) but not asymptomatic patients with magnetic resonance imaging lesions, even if there is evidence of acute infarction. Such patients were not enrolled in any of these studies and the subsequent results cannot be generalised to those who have no neurological correlate to their imaging findings.

**Dual antiplatelet therapy**

Antiplatelet therapy is the first secondary prevention opportunity in ischaemic stroke, with guidelines recommending aspirin administration within the first 48 h. In the past few years, two large randomised, double-blind, placebo-controlled trials, CHANGE (Clopidogrel in High-risk Patients With Acute Non-disabling Cerebrovascular Events) and POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischaemic Stroke Trial), have shown DAPT to be superior to aspirin monotherapy in a selected group of patients. Following a loading dose given within 12–24 h of symptom onset, aspirin and clopidogrel reduced the rate of recurrent ischaemic events at 90 days in POINT (hazard ratio (HR) for ischaemic stroke, myocardial infarction or death from ischaemic vascular causes 0.75, 95% confidence interval (CI) 0.59–0.95, \( P = 0.02 \)) and CHANCE (HR for stroke 0.68, 95% CI 0.57–0.81, \( P < 0.001 \)). Several enrolment criteria may affect the generalisability of these results to the broader stroke and TIA population. Unresolved issues include which patient population will benefit from DAPT, the ideal time frame of therapy and the ideal antiplatelet agents.

To be enrolled, patients with TIA required an ABCD² score ≥4. Patients with transient neurological symptoms otherwise consistent with a TIA but with a neuroimaging correlate should be considered as having had a stroke. Accordingly, we would recommend treating a transient event with positive neuroimaging as a minor stroke with National Institutes of Health Stroke Scale (NIHSS) score 0 and would support using dual antiplatelets in this population.

Patients with stroke were only enrolled if the severity was minor, defined as a NIHSS score ≤3. Patients with higher NIHSS scores may have a higher haemorrhagic transformation risk if DAPT is prescribed although this is unexplored.

Haemorrhage was the major safety end-point for both trials. In the POINT trial an increasing risk of major haemorrhage was demonstrated with longer duration of DAPT, with the optimum change-point for efficacy events at 21 days. The CHANCE protocol continued DAPT only for 21 days, with aspirin alone thereafter, and there was no increase in major haemorrhage during the 21-day period.

The POINT and CHANCE protocols required initiation of treatment within the first 12–24 h respectively. Both studies reported benefit in the second half of their recruitment time windows at least as good as in the first half. Progressive separation of the event curves after their respective recruitment time windows was observed in both studies, indicating an accumulation of prevented events in the first few days. This may suggest benefit from initiating treatment even after the first day post-stroke, although this concept requires further exploration.

Patients with an ipsilateral and significant internal carotid artery stenosis were not eligible for these studies if referral for endarterectomy was likely. However, in patients whose carotid stenosis was detected after enrolment, the protocol for the POINT trial required withholding antiplatelet therapy for surgery, which could be restarted post-operatively. This subset of patients was small and therefore it is unclear whether patients who are likely to receive carotid endarterectomy would benefit from DAPT. Conversely, there is limited evidence that the use of DAPT should preclude endarterectomy. In practice, if the local surgical preference is to operate on DAPT, it is reasonable to be prescribed even in the context of carotid stenosis. In addition, DAPT could be considered in patients who approximate the trial clinical criteria, even if carotid stenosis has not yet been excluded.
While the results of CHANCE and POINT have been practice changing, the shortcomings of clopidogrel have stimulated investigation into alternative antiplatelet agents. Ticagrelor has a faster onset of action and, unlike clopidogrel, its metabolism is largely unaffected by genetic polymorphisms. A trial of ticagrelor monotherapy versus aspirin administered within 24 h of high-risk TIA and minor stroke did not show superiority over aspirin.12 A currently recruiting international multicentre trial, THALES (Acute STroke or Transient Ischaemic Attack Treated With TicAgrelor and ASA for PrEvention of Stroke and Death), is assessing the use of ticagrelor and aspirin dual therapy against aspirin monotherapy in this scenario.13

In summary, it is reasonable to treat high-risk TIA (ABCD² score ≥24) and minor stroke (NIHSS ≤3) with a 300–600 mg clopidogrel load plus aspirin 100 mg on day 1, then DAPT with clopidogrel 75 mg daily plus aspirin 100 mg daily for 21 days prior to returning to a single antiplatelet agent for ongoing secondary prevention.

ESUS anticoagulation trials

In two recent large multicentre randomised controlled trials of patients with ESUS, anticoagulation was not superior to aspirin with respect to secondary ischaemic stroke prevention.3,14

NAVIGATE ESUS14 compared rivaroxaban 15 mg daily and aspirin 100 mg daily. The trial was terminated early by the data and safety monitoring committee, following the recruitment of 7213 patients, due to an excess risk of major bleeding with rivaroxaban (HR 2.72; 95% CI 1.68–4.39, P < 0.001), with no significant decrease in the risk of recurrent stroke (HR 1.07; 95% CI 0.87–1.33).

RE-SPECT ESUS3 compared dabigatran (150 mg twice per day or 110 mg twice daily depending on age and renal function) and aspirin 100 mg daily. There was no significant difference in the primary outcome of first recurrent stroke (HR 0.85; 95% CI 0.69–1.03). There was no significant difference in major bleeding (HR 1.19; 95% 0.85–1.66) although there was an increase in clinically relevant non-major bleeding in those who received dabigatran (HR 1.7; 95% CI 1.17–2.54).

The core concept of ESUS is being used as the basis for adding other markers to provide a more refined subpopulation that may benefit from anticoagulation. The ARCADIA study (AtRial Cardiopathy and Anti-thrombotic Drugs In Prevention After Cryptogenic Stroke) is investigating the use of apixaban in patients with ESUS plus markers of atrial cardiopathy (≥1 of: P-wave terminal force >5000 μV × ms in electrocardiogram (ECG) lead V₁, serum N-terminal prohormone of brain natriuretic peptide >250 pg/mL or left atrial diameter index ≥3 cm/m² on echocardiography).15 If positive, there may be ongoing interest in studying and treating patients with ‘ESUS plus’.

Taken together these trials indicate that patients with stroke meeting the current definition of ESUS should not routinely be anticoagulated, as there is no proven benefit and may be potential harm. The potential that anticoagulation benefits a subgroup of patients with ESUS is not yet clear.

Prolonged cardiac monitoring

AF has the potential to cause the most severe acute ischaemic strokes via large emboli and subsequent large vessel occlusion and there is strong evidence for long-term anticoagulation. However, NAVIGATE ESUS and RE-SPECT ESUS reaffirmed that AF must be documented prior to committing patients to anticoagulation.

Traditional cardiac monitoring for stroke assessment has involved a 24 h Holter monitor, with an overall AF detection rate of between 1% and 12%.16 Some stroke units use hard-wired telemetry beds, but the reliability is unproven and, in some studies, proved to be less sensitive than a 24 h monitor.16 Cardiac telemetry also introduces physical impracticalities, anxiety, extra workload and disruption to sleep that can be prompted by clinically irrelevant telemetry alarms.

Prolonged cardiac monitoring for up to 3 years post-stroke has been shown to have 10 times the rate of detection of paroxysmal AF (PAF) compared with short-term and intermittent monitoring.17 A 2015 systematic review of cardiac monitoring similarly supported a near doubled PAF detection rate with implantable or insertable cardiac monitors, also known as ILR compared with wearable devices.18 In 2019, ILR are small minimally invasive devices which can be implanted subcutaneously with a minor procedure. Thresholds can be set to alert patients and clinicians when PAF of 30 s or greater is detected. Implantation of ILR is therefore a practical option for searching for AF, especially in patients with a higher likelihood of harbouring PAF.

Similar thresholds have been imbedded into the ECG algorithms of the series 4 Apple Watch operating system update (watchOS 5.1), designed for the detection and notification of irregular cardiac rhythms. In the United States it has been cleared by the United States Food and Drug Administration as a class II item, meaning it is available, but not endorsed, as an alternative to standard medical care.19 When paired with the updated ECG software of an iPhone, it enables customers to record a tracing similar to a single-lead ECG. If the software is approved by the Therapeutic Goods Administration for inclusion or registration on the Australian Register of Therapeutic Goods, patients will be able to record ECGs from anticoagulation.

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at leisure and receive alerts for possible AF, advising them to seek medical advice. The accuracy of the device and ability to drive clinical management was examined in the Apple Heart Study, a prospective, single arm pragmatic study that enrolled more than 400 000 Apple customers. Results were announced at the American College of Cardiology annual scientific meeting in March 2019. Overall, the device was reasonably effective, with a positive predictive value of 71% of detecting AF on a single-dot ECG patch at the time of watch notification. A formal diagnosis of AF, to inform management decisions, still required confirmation via current accepted standards for diagnosis, such as a 12 lead ECG.

The importance of a temporal relationship between PAF and stroke and the duration of PAF required to confirm cardioembolic stroke risk is unclear. A growing body of evidence suggests that AF may be a marker of atrial cardiopathy or atrioatriopathy and it is this abnormal structure and mechanical dysfunction which leads to atrial thrombus formation. In this context, the detection of PAF may eventually be considered merely one of a list of factors that promote the patient from ESUS with no current therapeutic relevance to ‘ESUS plus’ requiring treatment. The conundrum of PAF timing and duration in stroke pathogenesis may in future become irrelevant.

Currently, prolonged cardiac monitoring using an ILR should be considered in patients in whom imaging findings are suggestive of a central embolic source, have no contraindication to anticoagulation and have no other aetiology such as carotid atherosclerosis warranting treatment. In practice, identifying a patient as having ESUS should prompt consideration for ILR implantation.

### Patent foramen Ovale

PFOs are seen in 20%–25% of the general population and are more common in patients with cryptogenic stroke, with estimates rising to approximately 40%–50%. There is biological plausibility that a PFO may lead to a stroke and there has therefore been interest in percutaneous closure of PFOs for several years.

The percutaneous closure of PFOs for the prevention of secondary stroke is now more strongly supported by evidence. Meta-analysis estimates of the benefit for PFO closure in the prevention of recurrent ischaemic stroke report a HR of 0.30 (95% CI 0.13–0.68, P = 0.004) compared with medical therapy with antiplatelets or anticoagulant and a HR of 0.19 (95% CI 0.06–0.54, P = 0.003) compared with antiplatelet therapy alone.

The success of these more recent trials is likely due to better devices and better patient selection. The newer trials used double-disk devices, and required high-risk features to be seen on echocardiography prior to PFO closure.

Patient selection on the recent positive trials included PFO with evidence of right–left shunting of microbubbles across the PFO or an atrial septal aneurysm. Of note, when considering PFO closure, the anatomical size of the PFO is not a selection criterion, so much as the dynamic changes that lead to microbubble shunting (Table 1).

Although enrolment was permitted up to 9 months after stroke and generally the maximum age was 60 in these trials, the mean age of patients in the trials was mid-40s to early 50s and the median time to PFO closure was 3–4 months after stroke. The trial results would best generalise to patients approximating these demographics.

Complications of PFO closure are rare (<1%) except for periprocedural AF, which was opportunistically detected in up to 6.6% of cases. However, the major clinical concern of AF is stroke, and the overall reduction in stroke rates with PFO closure indicates that periprocedural AF does not prevent net benefit from PFO closure.

The number needed to treat (NNT) to prevent one stroke per year in these trials ranged from 20 (DEFENSE-PFO, Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale) to 200 (RESPECT, Patent Foramen Ovale Closure or Medical Therapy After Stroke, follow-up). In the CLOSE study, although all 14 strokes occurred in the antiplatelet group, only one of these was disabling. These figures may suggest some degree of risk stratification, beyond applying the trial entry criteria is worth considering.

One risk stratification option is the risk of paradoxical embolism (RoPE) score. This score was designed to estimate the likelihood that a PFO will be present, and the likelihood that PFO has contributed to stroke. It ranges from low prevalence (23%) and likelihood of risk contribution (0%) with low scores (e.g. older patients with atherosclerotic risk factors) and a high prevalence (73%) and high likelihood (88%) with high scores (e.g. younger patients with no atherosclerotic risk factors). The likelihood of PFO-related stroke assessed with the RoPE score is conceptually the reciprocal of

| Table 1 Considerations for patent foramen ovale (PFO) closure |
|-----------------|-----------------|-----------------|-----------------|
| Young age†      | Stroke within the previous 9 months |
| Positive imaging evidence for ischaemic stroke |
| High risk features associated with PFO (e.g. right-to-left shunting with agitated saline contrast, or inter-atrial septal aneurysm) |
| No other cause found (e.g. arterial stenosis or atrial fibrillation) |

†A practical description of young age is given in the Concepts in Stroke Prevention section.
Figure 1  Stroke secondary prevention algorithm.  †Clopidogrel 300mg, aspirin 300mg loading dose. ‡See the discussion within the Concepts in Stroke Prevention section for further detail. §A trial of lifestyle modification can be considered where practical, prior to starting OHA (Diabetes Australia, National Guidelines). CEA, carotid endarterectomy; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; LAA, left atrial appendage; NAD, no abnormality detected; OHA, oral hypoglycaemic agent; PFO, patent foramen ovale; T2DM, type 2 diabetes.
atherosclerosis-related stroke. The elements of this score mirror those considered at the bedside in the assessment of the ‘young’ stroke patient. It should be noted that the RoPE score was not used to select patients in any PFO closure trials and that there is no established score for qualifying a patient for PFO closure. However, risk stratification with the RoPE score can be used to select high-risk patients in clinical practice.

There remain some areas of uncertainty with regards to the management of patients with PFO. It is unlikely that closure is of benefit in patients already committed to anticoagulation, for example due to AF. Such patients were excluded from the PFO closure trials.

In patients with PFO who do not proceed to PFO closure there is still insufficient evidence for anticoagulation in preference to antiplatelet therapy. No statistically significant benefit was seen in patients randomised to antiplatelet versus anticoagulation,27 rivaroxaban 15 mg daily14 or dabigatran.1 There has been a meta-analysis showing an odds ratio for stroke of 0.48 (95% CI 0.24–0.96, P = 0.04) in favour of anticoagulation over antiplatelet therapy in ESUS patients who have PFO31 but intracerebral and other haemorrhage rates were not reported so the net clinical benefit is unclear.

Percutaneous closure of a PFO is therefore a reasonable approach in the young patient if there is a recent imaging-confirmed stroke, high-risk features on echocardiography and if no other specific stroke prevention therapy is already indicated.

**Left atrial appendage occlusion**

The advent of DOAC has vastly simplified anticoagulation for secondary stroke prevention in AF. However, a significant number of patients with AF will not tolerate or have absolute contraindications to anticoagulation. This problem has prompted investigation into surgical alternatives to reduce cardioembolism in AF, focusing on LAA as a source of the majority of emboli in this context. A systematic review32 estimated that ~90% of AF-related thrombi are found in the LAA, and that ~75% of embolic events in AF are due to atrial thrombi, such that about 68% of embolic events in chronic AF can be attributed to thrombi in the LAA. This has prompted the development of various devices for percutaneous LAA occlusion over the past decade.

In the PREVAIL33 study, LAA occlusion was non-inferior to warfarin for the prevention of stroke and other events. A subsequent 2015 meta-analysis34 incorporating long-term follow-up data showed similar rates of ischaemic events between groups but a significantly higher number of haemorrhagic strokes in the warfarin group. Therefore, a LAA occlusion strategy may be reasonable based on a desire to avoid anticoagulation whether this be clinical or otherwise. However, several caveats exist which have not yet been resolved. First, the optimum antithrombotic therapy after LAA occlusion is unclear. The use of at least 6 months of warfarin after LAA occlusion was common in the trials and thus a contraindication to anticoagulation was a trial exclusion criterion. Second, detection of a device related thrombus is difficult and registry data suggest incidence rates which vary from 5% to 25%, depending on the device and post-insertion antithrombotic regimen.38 Finally, there are no data to compare LAA occlusion to DOAC with respect to long-term haemorrhagic stroke risk.

Further research is needed into the appropriate application of LAA occlusion and periprocedural management in the era of DOAC. However, currently, LAA occlusion could be considered in those patients in whom avoidance of anticoagulation would be preferred but could tolerate a short period of DAPT or DOAC. This may not be an ideal approach in those patients at very high risk of intracerebral haemorrhage, for example patients with advanced cerebral amyloid angiopathy.

**Conclusion**

Stroke secondary prevention has improved significantly in recent years. ILR, PFO occlusion devices and LAA occlusion devices are now included on the Department of Health Prostheses List36 and accessibility of these devices has therefore improved. However, the overlap in the timing of design and recruitment of recent trials has created complexity when applying the evidence in the stroke unit. A suggested algorithm focusing on the topics discussed in this review is presented in Figure 1.

DAPT is effective when given soon after high-risk TIA or minor stroke but should be downgraded to monotherapy after 21 days. Anticoagulation for patients with ESUS is not superior to antiplatelet therapies but subgroups of ESUS who do benefit from anticoagulation may exist within current datasets or may be identified in future studies. Prolonged cardiac monitoring with ILR to identify PAF is a valid approach for ESUS patients. PFO closure in young patients is particularly indicated after recent stroke if there are high-risk features on the echocardiogram. LAA occlusion can be considered in patients with AF who can tolerate a short period of anticoagulation but in whom there is a desire to avoid long-term anticoagulation.
References


Secondary prevention of ischaemic stroke


**Position Paper**

**Diagnosis, management and prevention of Candida auris in hospitals: position statement of the Australasian Society for Infectious Diseases**

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**Key words**

*Candida auris*, mycology, microbiology, antifungal, infection prevention.

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**Abstract**

*Candida auris* is an emerging drug-resistant yeast responsible for hospital outbreaks. This statement reviews the evidence regarding diagnosis, treatment and prevention of this organism and provides consensus recommendations for clinicians and microbiologists in Australia and New Zealand. *C. auris* has been isolated in over 30 countries (including Australia). Bloodstream infections are the most frequently reported infections. Infections have crude mortality of 30–60%. Acquisition is generally healthcare-associated and risks include underlying chronic disease, immunocompromise and presence of indwelling medical devices. *C. auris* may be misidentified by conventional phenotypic methods. Matrix-assisted laser desorption ionisation time-of-flight mass spectrometry or sequencing of the internal transcribed spacer regions and/or the D1/D2 regions of the 28S ribosomal DNA are therefore required for definitive laboratory identification. Antifungal drug resistance, particularly to fluconazole, is common, with variable resistance to amphotericin B and echinocandins. Echinocandins are currently recommended as first-line therapy for infection in adults and children ≥2 months of age. For neonates and infants <2 months of age, amphotericin B deoxycholate is recommended. Healthcare facilities with *C. auris* should implement a multimodal control response. Colonised or infected patients should be isolated in single rooms with Standard and Contact Precautions. Close contacts, patients transferred from facilities with endemic *C.
**Background**

*Candida auris* is an emerging multi-drug resistant organism (yeast) that has caused several hospital outbreaks overseas. Sporadic infections also occur. Infections have high mortality and the organism can be misidentified by laboratories. We review the evidence regarding this organism, focusing on laboratory diagnosis, clinical management and infection prevention in hospitals. We also provide consensus recommendations for clinicians and microbiologists in Australia and New Zealand in preparation for, or response to, the local emergence of *C. auris*. These recommendations should be adapted according to clinical and/or operational requirements and interpreted within the context of guidance from jurisdictional and national authorities.

**History and emergence**

*Candida auris* sits in the Kingdom Fungi, and belongs to the Family (clade) *Metschnikowiaceae*. The species epithet (*auris*) is Latin for ‘of the ear’, the site from which the type-strain was first isolated in Japan in 2009. Its closest phylogenetic relationship is with *Candida haemulonii*.

Whole genome sequencing (WGS) data indicate near-simultaneous emergence of *C. auris* and spread of independent clones, rather than global transmission of one clone. Four main geographic-specific clades have been described – South Asia, South Africa, South America and East Asia – each separated by many tens of thousands of single nucleotide polymorphisms.

The first Australian detection of *C. auris* (South Africa clade) occurred in Perth in 2015. Since mid-2018, further detections have occurred in Victoria (three patients), New South Wales (three patients) and Western Australia (one patient).

**Epidemiology**

Since the first report, *C. auris* has been identified retrospectively from superficial ear swabs in South Korea, where the first cases of candidaemia were also reported in 2011. Since 2010, invasive candidiasis cases were reported from India, Venezuela, USA and UK, with isolates now described in at least 32 countries on six continents (Fig. 1). A large burden of infection and colonisation has been reported from the USA, with 725 confirmed clinical cases, 30 probable cases and an additional 1474 colonised patients as of 30 June 2019. In South Africa, 1692 confirmed or probable *C. auris* cases were identified from October 2012 to November 2016. Of 1579 patients with available data, 29% had invasive disease. An Indian report identified 350 isolates from 10 hospitals collected between 2009 and 2017. To date, most cases have been reported in adults, with only 29 paediatric cases identified: 23 with candidaemia (including 17 neonates) from South Korea, India and Venezuela; three with chronic otitis media from South Korea and three from unspecified sites.

Healthcare outbreaks have been reported from at least eight countries. Some outbreaks from Europe and USA are summarised in Table 1. Where tested, healthcare workers (HCW) were not found to be colonised during outbreaks in the UK and Spain.

Acquisition of *C. auris* is usually healthcare-associated in high-risk units. *C. auris* infections have a slight male preponderance. Underlying immunocompromise or chronic disease (e.g. diabetes, lung disease, renal failure, cardiovascular disease, malignancy) are frequently observed. Use of broad-spectrum antibiotics, antifungals, invasive medical devices or invasive procedures generally precede infection. Intensive care patients, pre-term neonates and elderly patients are recognised risk groups. Environmental shedding and persistence of the organism mean that ward contact or close contact with *C. auris* cases is recognised as a risk factor for acquisition, particularly following exposure to healthcare systems in endemic countries. Most patients have had extensive healthcare exposure, with a median of 19 days from hospitalisation to acquisition.

**Clinical syndromes**

From 2013 to 2017, 620 cases of *C. auris* were reported in the European Economic Area, with 75% colonisation only, 18% candidaemia, 7% infection at other sites and 0.6% unknown colonisation/infection status. Conversely, a systematic review of over 700 global cases from 2012 to 2017 demonstrated the majority of isolates were obtained from blood cultures, central line tip cultures or deep tissue samples, whilst urine isolates were...
less frequent.\textsuperscript{12} Pericarditis,\textsuperscript{26} central nervous system (CNS) shunt infection\textsuperscript{27} and donor-derived infection after lung transplantation have also been described.\textsuperscript{28}

Colonisation of skin and mucosal surfaces often occurs in outbreaks.\textsuperscript{19} \textit{C. auris} was isolated from wounds, rectal and pharyngeal swabs, respiratory samples and urine during screening in Spanish and UK outbreaks, and persisted for weeks.\textsuperscript{19,21} The ratio of colonised to infected patients was 2–3:1.\textsuperscript{19,21} Colonisation reappeared after apparent clearance in some cases.\textsuperscript{19} The proportion of candidaemia cases varied with different outbreak reports (Table 1). In a Spanish outbreak, metastatic complications of candidaemia such as bone and heart valve infection occurred in 12\% of patients.\textsuperscript{21} Thirty-day mortality for invasive candidiasis was 41.4\%.\textsuperscript{21} Another study indicated in-hospital mortality as 59\% and a systematic review reported a crude mortality rate of 30\% for patients infected or colonised with \textit{C. auris},\textsuperscript{12} with similar outcomes in children and neonates.\textsuperscript{29}

\section*{Laboratory diagnosis}

Culture-based approaches remain the mainstay of laboratory diagnosis of \textit{C. auris}. All yeast isolates should be

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Country & City & Institution & Period & Ongoing at time of report & Total cases & Infection cases & Candidaemia cases \\
\hline
UK\textsuperscript{19} & London & Royal Brompton Hospital & April 2015 to July 2016 & Yes & 50 & 22/50 & 9/50 \\
UK\textsuperscript{20} & Oxford & Oxford University Hospitals & February 2015 to August 2017 & No & 70 & 7/70 & 4/70 \\
Spain\textsuperscript{21} & Valencia & Hospital Universitari i Politècnic La Fe & April 2016 to January 2017 & Yes & 140 & 41/140 & 41/140 \\
USA\textsuperscript{22} & New York City & Multiple & May 2013 to June 2017 & Yes & 112 & Unclear & 31/112 \\
\hline
\end{tabular}
\caption{Summary of some \textit{Candida auris} outbreaks in Europe and USA}
\end{table}
accurately identified to the species level when obtained from a normally sterile site or when isolated from non-sterile sites and one of the following apply:

- When clinically indicated for patient care.
- When C. auris has been detected in the same healthcare facility.
- When the patient has had an overnight stay in an overseas healthcare facility.

C. auris will be included in the Australian National Alert System for Critical Antimicrobial Resistances (CARAlert) during 2019.

C. auris grows on routine laboratory media and mycological media (e.g. Sabouraud’s dextrose agar), but may take up to 10 days. To increase sensitivity, several inexpensive in-house broth enrichment methods have been described that exploit this species’ salt-tolerance and ability to grow at 42°C. The addition of 10% sodium chloride, gentamicin, chloramphenicol and either dulcitol, mannitol or dextrose to Sabouraud’s (or yeast nitrogen base) broth are reported to significantly increase sensitivity and specificity. The Centers for Disease Control and Prevention (CDC), USA recommends the use of a 10% salt Sabouraud’s dulcitol (SSD) broth (with added chloramphenicol and gentamicin) medium (see ‘Microbiological methods for screening’). Australian and New Zealand laboratories may choose to only culture specimens onto solid media or to utilise broth enrichment, depending on laboratory capability to provide the broth media.

Phenotypic identification methods

Microscopy and culture

C. auris exhibits oval-elongated budding yeast forms with rare pseudohyphae, and is germ-tube negative. Conversely, C. haemulonii and Candida duobushaemulonii form pseudohyphae with blastoconidia and do not grow at 42°C. C. auris colonies are white-to-cream in colour on Sabouraud dextrose agar. On CHROMagar Candida (Becton Dickinson & Company, Baltimore, MD, USA) or Agar Candida ID2 (CAN2) medium (bioMérieux, Marcy l’Etoile, France) colonies are beige/white, then light pink to red or purple by day 4 of growth (Fig. 2). Chromogenic agars cannot be used for primary identification, but are useful to highlight colonies suspicious for C. auris, especially from mixed cultures.

Biochemical identification

In Australia and New Zealand, some laboratories undertake speciation of a ‘presumptive’ Candida using conventional phenotypic methods that misidentify C. auris as another Candida species (Table 2), most frequently C. haemulonii. In one study, approximately 90% of isolates reported as C. haemulonii by the VITEK 2 system (bioMérieux) were C. auris. The API 20C AUX system (bioMérieux) misidentifies C. auris as Rhodotorula glutinis (Table 2). Biochemical methods are insufficient for definitive species identification. The recently released Vitek 2 YST software (v8.01 and later) may correctly identify C. auris strains belonging to clades from Africa and South Asia, but not East Asia. Vitel 2 identifications of C. haemulonii or C. duobushaemulonii using older software versions require further work-up for correct identification.

Matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS) identification

Spectral databases for clinical laboratories

MALDI-TOF MS provides reliable identification of C. auris, providing the spectral library contains validated reference spectra for all clades. Most clinical laboratories in Australasia use either the Vitek MS (bioMérieux) or Bruker Biotyper (Bruker Daltonics, Bremen, Germany) instruments. Previously, the Biotyper system provided a ‘No reliable identification’ result, whilst the Vitek MS misidentified the organism as C. haemulonii or Candida lusitaniae. With both systems, subsequent incorporation of updated databases containing validated C. auris spectra
Currently, in USA, accurate identification including spectra from diverse collections of strains. Phenotypic identification with databases now contain libraries, ideally supplemented by in-house-generated MALDI-TOF MS-based identification. Using updated commercial MALDI TOF MS database libraries, ideally supplemented by in-house-generated spectra, C. auris isolates can be identified to species level (log score ≥ 2.00) with 100% sensitivity and specificity. However, if an older database without representative isolates from all clades is used, log scores of <2.00 may result. Nonetheless, numerous studies have evaluated the Bruker system against MALDI-TOF MS in identifying C. auris from single colonies in 2.5 and 2 h respectively, but sensitivity was unconfirmed for all clades. Also, a cultured isolate was still required (2–14 days). A recently developed real-time PCR assay targeting the ITS2 region could rapidly identify all 44 C. auris isolates from surveillance samples within 4 h. The assay was highly specific, had a limit of detection of 1 colony-forming unit/polymerase chain reaction (CFU/PCR), and detected isolates from all clades. For culture-positive swabs (n = 49) and sponges (n = 58), the sensitivity was 89 and 100% respectively. Additionally, this assay detected C. auris DNA from a few culture-negative samples.

### Performance of MALDI-TOF MS

Using updated commercial MALDI TOF MS database libraries, ideally supplemented by in-house-generated spectra, C. auris isolates can be identified to species level (log score ≥ 2.00) with 100% sensitivity and specificity. However, if an older database without representative isolates from all clades is used, log scores of <2.00 may result. Nonetheless, numerous studies have evaluated both MALDI-TOF MS systems for C. auris identification with overall satisfactory results. Addition of the ClinProTools software to the Bruker system provides superior discrimination. Generally, previous studies showed that the Bruker system is superior to the Vitek MS in identifying C. auris. Inconsistent MALDI-TOF MS-based identification reflects strain variation, emphasising the need to include strains from all clades in databases. Laboratories should consider whether or not the database in use is adequate for reliable identification, and implement other confirmatory methods (e.g. DNA sequencing) as required.

### Extraction protocols

Increasingly, clinical laboratories perform protein extractions using direct on-plate rather than full tube extraction methods. For C. auris, one study demonstrated that on-plate formic acid extraction was the most time and cost-efficient method. However, another study using the Bruker RUO system revealed direct on-plate extractions resulted in low score matches for 50% of strains and the remaining 50% were unidentifiable. Partial extraction methods are reported by others to give reliable identification. Local experience indicates that at least partial extractions are required to consistently achieve log scores of ≥2.00 (authors: personal communication).

### Molecular detection and identification

Sequencing of the internal transcribed spacer (ITS) regions and/or the D1/D2 regions of the 28S ribosomal DNA provides species confirmation and phylogenetic information. One study demonstrated that conventional and real-time PCR assays targeting the ITS2 region could rapidly identify all 44 C. auris isolates from single colonies in 2.5 and 2 h respectively, but sensitivity was unconfirmed for all clades. Also, a cultured isolate was still required (2–14 days). A recently developed real-time PCR assay targeting the ITS2 region detects C. auris from surveillance samples within 4 h. The assay was highly specific, had a limit of detection of 1 colony-forming unit/polymerase chain reaction (CFU/PCR), and detected isolates from all clades. For culture-positive swabs (n = 49) and sponges (n = 58), the sensitivity was 89 and 100% respectively. Additionally, this assay detected C. auris DNA from a few culture-negative samples.

In-house assays have significant utility, but locally available, simple, low-cost, well-validated commercial assays are also needed. Both the Fungiplex Candida Auris RUO real-time PCR assay (Bruker Daltonics) and the GPS™ MONODOSE dic-e-qPCR tests (Alicante, Spain) could potentially meet these requirements, and are undergoing evaluation.

### Genotyping

Amplified fragment length polymorphism analysis, multilocus sequence typing and pulsed-field gel electrophoresis have all been applied successfully to differentiate outbreak strains. However, WGS has superior discriminative power and is the preferred method for simultaneously identifying and genotyping strains.
Long read sequencing has been used to investigate hospital outbreaks.\(^{20,53}\) Although WGS can offer a shorter turnaround time (8–72 h) than other typing methods, it requires extra bioinformatic expertise and is more expensive.

**Quality Assurance in Australia and New Zealand**

In December 2017, the Royal College of Pathologists of Australasia Mycology Quality Assurance Program distributed *C. auris* to 71 laboratories within Australia and New Zealand. Only 65% of participants correctly identified the isolate to species level. Misidentifications included *Candida parapsilosis* (\(n = 2\) participants), *Candida sake* (2), *Candida famata/Debaryomyces hansenii* (2), *Candida glabrata* (1) and *C. haemulonii* (1). Incorrect or incomplete identifications were predominantly among those laboratories using the Vitek MALDI-TOF MS and either the API 20C or ID 32C biochemical kits (bio-Merieux). Most laboratories that correctly identified *C. auris* were utilising the Bruker MALDI-TOF MS (28/29; 97%), Vitek 2 YST (12/18; 67%) and ITS region DNA sequencing (2/2; 100%). A subsequent survey in 2018 distributed the same *C. auris* isolate and demonstrated improved results, with 61 of 70 laboratories (87%) providing correct identification. This improvement could be attributed to the updated databases of the Vitek MALDI-TOF MS and Vitek 2 YST systems.

**Antifungal resistance**

No clinical breakpoints have been endorsed for *C. auris* by the Clinical and Laboratory Standards Institute (CLSI) or the European Committee for Antimicrobial Susceptibility Testing (EUCAST). However ‘tentative breakpoint’ MIC (in mg/L)\(^{54}\) developed by the CDC (for use with CLSI testing methodology) are: fluconazole \(\geq 32\); amphotericin B \(\geq 2\); anidulafungin \(\geq 4\); micafungin \(\geq 4\); caspofungin \(\geq 2\). These are supported by proposed MIC epidemiological cutoff values.\(^{55}\) Antifungal susceptibility testing is recommended for all isolates.\(^{54}\)

Based on a meta-analysis of minimum inhibitory concentration (MIC) of 742 global *C. auris* isolates,\(^{12}\) when applying these tentative breakpoints, overall ‘resistance’ rates were fluconazole 44%; amphotericin B 16%; caspofungin 3.5% and anidulafungin and micafungin 1.3%. For antifungals lacking breakpoints, the following proposed epidemiological cutoff value\(^{54}\) non-wild-type frequencies were: voriconazole 13%; flucytosine 2%; itraconazole 1.8%; isavuconazole 1.5% and posaconazole 1.4%.\(^{12}\)

Antifungal susceptibility profiles of *C. auris* vary between geographical regions, where clonal propagation of isolates with specific point mutations in the ERG11 and FKS1 genes are described. *C. auris* strains from East Asia are comparatively ‘susceptible’.\(^{12}\) ‘Resistance’ was more common among 350 isolates from India: fluconazole 90%, amphotericin B 8%, anidulafungin and micafungin 2%. Moreover, 25% were ‘resistant’ to two or more drug classes, and 13% were multi-azole ‘resistant’.\(^{15}\) Similarly, in New York, 98% of isolates were ‘resistant’ to fluconazole, and 25% ‘resistant’ to both fluconazole and amphotericin B.\(^{22}\) In Spain, all isolates were fluconazole- and voriconazole-‘resistant’, whilst none was ‘resistant’ to echinocandins or amphotericin B.\(^{21}\) In an UK outbreak most strains were ‘susceptible’ to echinocandins.\(^{19}\)

The reference standards for antifungal susceptibility testing are the CLSI broth microdilution\(^{56}\) or EUCAST broth microdilution,\(^{57}\) but commercial methods such as Sensititre YeastOne (Trek), Vitek 2 YST AST (bio-Merieux) and Etest (bioMerieux) are more commonly utilised by diagnostic laboratories because they are more user friendly. However, amphotericin B and caspofungin MIC generated by the Vitek 2 YST AST and Etest are often variable in comparison to the CLSI standard.\(^{26,36}\) Isolates with MIC values derived from either of these methods should be referred for confirmation using a reference method. Currently in Australia and New Zealand, only CLSI-based broth microdilution methods are used. As such, only the CLSI-based interpretive criteria should be utilised.

**Microbiological methods for screening**

Methodologies for screening specimens are identical to culture of *C. auris* from infected sites. If the direct plate culture method is used, 10 days of incubation is required before a negative result may be issued. Hence, many experts recommend broth enrichment as described above. For specimen collection, the CDC uses the BD ESwab kit (modified liquid Amies medium; Becton Dickinson, Sparks, MD, USA). Swabs are placed in 2 mL- aliquots of 10% SSD broth containing chloramphenicol and gentamicin, incubated at \(-250\) rpm at 40°C and inspected daily for 5 days. If the broth becomes turbid, a 10 μL loop is used to inoculate CHROMagar *Candida*, whereas if the broth remains clear 100 μL is inoculated. Plates are incubated at 37°C for 48 h and examined for colonies as described above.\(^{33}\)

Commercial real-time PCR assays offer potential for screening (see ‘Molecular detection and identification’ above). In the USA and Europe, the T2 Candida assay (T2 Biosystems, Lexington, MA, USA) has been used to rapidly detect *C. auris* in composite axilla/groin swabs.
with a sensitivity of 89% and a specificity of 92% compared with culture.\textsuperscript{59} However, this assay is currently unavailable in Australasia.

Refer to Box 1 for a summary of laboratory diagnosis recommendations.

**Box 1 Summary of laboratory diagnosis recommendations**

- **R1.** Culture-based methods to detect and grow *Candida auris* require 10 days of incubation to call a ‘negative’ result if direct-plating is used. Broth enrichment methods are recommended.
- **R2.** Laboratories using only biochemical identification systems to identify *Candida auris* should refer any isolates for definitive identification.
- **R3.** Definitive identification may be achieved by MALDI-TOF MS provided an appropriate database containing *C. auris* spectra is used. When using libraries which do not contain spectra representing all clades, log scores of <2.00 are frequent and caution should be exercised when interpreting a log score of <2.00. A minimum of partial protein extraction should be undertaken.
- **R4.** Definitive identification may also be achieved by DNA sequencing or whole genome sequencing.
- **R5.** Antifungal susceptibility testing should be performed for all *C. auris* isolates and MIC values interpreted with caution. Laboratories using the VITEK 2 YST and Etest methods should refer the isolate for susceptibility testing using a method endorsed by CLSI or EUCAST.
- **R6.** Because *Candida auris* comprises four clades with phenotypic differences that impact on accurate identification and antifungal drug susceptibility, laboratories characterising *C. auris* strains should consider appropriate comparisons with strains of known pedigree.

R, recommendation.

### Clinical management

*Candida auris* infections are associated with high rates of treatment failure.\textsuperscript{59-61} Reported crude mortality rates vary from 30 to 59% in patients with candidaemia,\textsuperscript{6,12,62} although this may relate to the severity of the underlying disease and the persistence of candidaemia with this organism.\textsuperscript{21,14,63} No randomised studies have quantified the effectiveness of any specific antifungal drug for *C. auris* infection.\textsuperscript{59,60} Therefore, recommended treatment regimens for *C. auris* infections are unvalidated.\textsuperscript{54} Pharmacokinetic and pharmacodynamic (PK/PD) studies of existing antimicrobial agents demonstrate the MIC breakpoints of antifungals for other selected *Candida* species probably apply to *C. auris*.\textsuperscript{64} Indeed, strong relationships exist between PK/PD parameters and treatment outcomes for most systemic antifungal drugs and the dose-effect of antifungals against *C. auris* is generally proportional to the MIC.\textsuperscript{64} Clinical trials of novel antifungals for *Candida* spp. are in progress.

### Treatment

Echinocandins (Table 3) are currently recommended in adults and children ≥2 months of age for both empirical (i.e. *C. auris* suspected) and initial (i.e. *C. auris* confirmed but awaiting susceptibility results) therapy of infection,\textsuperscript{24,55,59,60,64} given in vitro activity. and low rates of primary resistance. For neonates and infants <2 months of age, the initial treatment of choice is amphotericin B deoxycholate (1 mg/kg daily). If there is no response, consider liposomal amphotericin B (5 mg/kg daily).\textsuperscript{60} Premature infants or neonates with invasive candidiasis are likely to have disseminated disease, specifically haematogenous meningoencephalitis, until proven otherwise. Therefore, empiric therapy should penetrate the cerebrospinal fluid (CSF) adequately. Echinocandins have limited CSF penetration, although dose-dependent penetration of micafungin into neonatal CSF is reported.\textsuperscript{67} Despite this, echinocandins should be administered to neonates and young infants only when CNS disease is excluded or if other recommended treatment fails (Table 4).\textsuperscript{60} In neonates and children there are limited data regarding the PK/PD, safety and efficacy of anidulafungin. Therefore, if echinocandins are prescribed, micafungin or caspofungin is favoured.\textsuperscript{29,68}

Choice of directed antifungal therapy should be individualised based on susceptibility results and clinical site(s) of disease. *C. auris* can develop resistance rapidly, hence, follow-up cultures should be performed and any subsequent isolates should undergo repeat susceptibility testing.

### Table 3  Empirical and initial therapy for *Candida auris* infection\textsuperscript{50,65}

<table>
<thead>
<tr>
<th>Echinocandin</th>
<th>Adult dosing</th>
<th>Paediatric dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(children 2 months to 17 years old)</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>Loading dose 200 mg i.v., then 100 mg i.v. daily</td>
<td>Not approved in children</td>
</tr>
<tr>
<td></td>
<td>Loading dose 70 mg i.v., then 50 mg i.v. daily</td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Loading dose 70 mg i.v., then 50 mg i.v. daily</td>
<td>Loading dose 70 mg/m²/day I.V., then 50 mg/m²/day I.V. (based on body surface area)</td>
</tr>
<tr>
<td></td>
<td>Loading dose 70 mg/m²/day I.V., then 50 mg/m²/day I.V. (based on body</td>
<td></td>
</tr>
<tr>
<td></td>
<td>surface area)</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>100 mg i.v. daily</td>
<td>Children &lt;40 kg: 2–4 mg/kg/day I.V.†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children &gt;40 kg: 100–200 mg/day I.V.‡</td>
</tr>
</tbody>
</table>

\textsuperscript{†}Patient’s body surface area as calculated by the Mosteller formula,\textsuperscript{56} which is: BSA (m²) = \sqrt{[\text{height (cm)} \times \text{weight (kg)}/3600]}. \textsuperscript{‡}Option to use higher dose if inadequate initial response.
and/or if other recommended treatment fails.

The body surface area as calculated by the Mosteller formula, which is: BSA (m²) = \sqrt{\text{height (cm)} \times \text{weight (kg)}/3600}.

Oral antifungals

*C. auris* is often resistant to azole antifungals, hence, oral treatment options are limited. Azoles are contraindicated unless testing confirms susceptibility. Posaconazole appears the most potent azole *in vitro*, closely followed by isavuconazole. However, a study not including *C. auris* isolates did not demonstrate the non-inferiority of isavuconazole to caspofungin for primary treatment of invasive candidiasis.

Management of persistent candidaemia

Both recurrent and persistent *C. auris* candidaemia are reported. Patients clinically unresponsive to echinocandins or with persistent candidaemia >5 days should be switched to an alternative antifungal regimen based upon susceptibility testing results.

Combination therapy

The efficacy of combination antifungals in treatment of *C. auris* infection has not been established, hence, there is no recommendation for combination therapy. Combination therapy may be necessary for urinary tract or CNS infections. *In vitro* studies demonstrate synergy between micafungin and voriconazole, and solumetabolite withazole antifungals for selected strains. Animal-model data imply that micafungin-based combination therapies are promising.

Adjunctive measures

In unselected cases of candidaemia, infectious diseases consultation is associated with improved patient survival. Whilst unstudied for *C. auris*, we recommend infectious diseases consultation. As for all invasive infections with *Candida* spp., although not specifically studied for *C. auris*, adjunctive measures for *C. auris* bloodstream infection should include:

1. Ophthalmological examination following dilation, preferably by an ophthalmologist, to exclude intraocular infection;
2. Follow-up blood cultures to establish clearance of candidaemia;
3. Two weeks of therapy after clearance of candidaemia in patients without metastatic complications; and,

Biofilms and antifungals

The biofilm-generating capability of *C. auris* is less than that of *Candida albicans*, but it remains an important virulence factor. Biofilms form a physical barrier against antifungal agents and disinfectants. The limited published data on biofilm-active antifungals are conflicting. Therefore, no specific recommendations can be made. Refer to Box 2 for a summary of clinical management recommendations.

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**Table 4** Echinocandin dosing for *Candida auris* infections in neonates and infants aged <2 months

<table>
<thead>
<tr>
<th>Echinocandin</th>
<th>Neonatal dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anidulafungin</td>
<td>Not approved in neonates</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>25 mg/m²/day i.v. (based on body surface area)</td>
</tr>
<tr>
<td>Micafungin</td>
<td>10 mg/kg/day i.v.</td>
</tr>
</tbody>
</table>

†Amphotericin B deoxycholate (1 mg/kg daily) is the recommended first-line treatment of invasive candidiasis in neonates and young infants aged <2 months. Echinocandins are provided as alternative treatment options for invasive candidiasis only when CNS disease is excluded, and/or if other recommended treatment fails. ‡Patient’s body surface area as calculated by the Mosteller formula, which is: BSA (m²) = \sqrt{\text{height (cm)} \times \text{weight (kg)}/3600}.
**Infection prevention and control measures**

Various organisations have issued guidelines for *C. auris* infection prevention and control (Table 5). When *C. auris* is identified in healthcare facilities, a multidisciplinary management team should be formed to ensure appropriate resourcing. Regular communication with executive sponsors should occur to optimise the implementation of protocols for risk mitigation. Patients with infection or colonisation should be educated regarding the rationale for infection control measures.

**Case isolation/transmission-based precautions**

**Patient placement**

Patients colonised or infected with *C. auris* should be placed in a single room and managed using Standard and Contact Precautions. Cohorting of patients with *C. auris* is permitted. The duration of colonisation is unclear. Consequently, it is not recommended that patients are removed from isolation. If a patient is transferred to another department within a facility (e.g. radiology), the receiving department should be notified of the patient’s status and precautions taken to prevent transmission. Where possible, patients undergoing procedures should be scheduled last on the day’s list.

For patients with colonisation or infection, additional precautions should be implemented wherever possible:

- Minimise the number of staff caring for these patients. (Allocation of dedicated staff should be strongly considered if transmission occurs despite other interventions.)
- Dedicated bathroom facilities (or commode or pans) should be provided.
- Single-patient use items/patient care equipment should be used wherever possible.

**Pre-emptive isolation**

Patients at high-risk of *C. auris* colonisation require pre-emptive isolation pending screening results. High-risk patients include close contacts of *C. auris* patients and patients transferred from a hospital with endemic *C. auris* or admitted following at least an overnight stay in an overseas healthcare institution in the previous 12 months.

Close contacts of patients with *C. auris* are defined as current room contacts and past room contacts within the previous month (including those at other wards/facilities). In one outbreak, close contacts of *C. auris* cases were de-isolated after three consecutive negative screens but thereafter screened weekly until discharge. One contact became positive after three consecutive negative screens. Close

<table>
<thead>
<tr>
<th>Health organisation</th>
<th>Environmental disinfection</th>
<th>Decolonisation procedure</th>
<th>Hand hygiene procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers for Disease Control and Prevention</td>
<td>Daily and terminal cleaning with use of an EPA-registered hospital-grade disinfectant effective against <em>C. difficile</em> spores</td>
<td>No recommendations</td>
<td>Use alcohol-based hand sanitiser or hand washing with soap and water, before and after donning gloves</td>
</tr>
<tr>
<td>Public Health England</td>
<td>Terminal cleaning with use of a hypochlorite at 1000 ppm. Equipment should be cleaned according to manufacturer’s instructions</td>
<td>No recommendations</td>
<td>Hand washing with soap and water followed by alcohol-based hand sanitiser on dried hands, before and after donning gloves</td>
</tr>
<tr>
<td>European Centre for Disease Prevention and Control Centre for Opportunistic, Tropical and Hospital Infections (South Africa)</td>
<td>Terminal cleaning with disinfectants with certified antifungal activity</td>
<td>No recommendations</td>
<td>No recommendations</td>
</tr>
<tr>
<td>Pan American Health Organisation/World Health Organisation</td>
<td>Daily and terminal cleaning with soap and water followed by 0.1% bleach. Clean, disinfect, or sterilise equipment and appliances as per the type of material, after use by the patient. Machine wash linens and clothes</td>
<td>No recommendations</td>
<td>No recommendations</td>
</tr>
</tbody>
</table>
contacts can be de-isolated after three consecutive negative screens taken at least 24 h apart.89

Environmental cleaning and disinfection

Environmental contamination
The environment plays a significant role in the transmission of C. auris. In one outbreak, root cause analysis suggested an unidentified environmental source and that a minimum contact of ≥ 4 h was necessary for acquisition.19 C. auris has been isolated from the mattress, bedside table, bed rail, chair and window sill in the room of a patient with persistent C. auris infection;62 and the air, floor, walls, trolleys, radiators, equipment monitors, keypads, ventilators, electrocardiogram leads and other medical equipment in outbreak settings.19,21,83 Multi-use patient equipment items have been contaminated, including a pulse oximeter and a patient hoist.84 One outbreak was linked to reusable axillary temperature probes.20 C. auris may persist on moist or dry surfaces for 7 days85 and sampling of environmental surfaces during an outbreak also identified C. auris on beds and equipment for up to seven days.83 In another study, C. auris remained viable on plastic surfaces for 14 days, and was still detectable at 28 days.32

Cleaning and disinfection agents
In vitro studies have evaluated the effectiveness of various cleaning products against C. auris.76 There is conflicting evidence regarding the efficacy of quaternary ammonium compounds for C. auris,83,86 and their use is discouraged. Several studies have demonstrated that chlorine-based disinfectants (concentrations from 3900 to 20 000 ppm chlorine) show greater efficacy against C. auris.83,86–89 Other products resulting in ≥5 log10 CFU reduction include hydrogen peroxide (1.4%), peracetic acid (1200 ppm) with hydrogen peroxide (<1%) and acetic acid, and improved hydrogen peroxide (0.5%).86 Ethyl-alcohol (29.4%) produced a <3 log10 CFU reduction.86

Non-touch disinfection techniques
UV-C light (254 nm with 10 min exposure time) is less effective for C. auris than methicillin-resistant Staphylococcus aureus although increasing exposure times to 20–30 min significantly increased the efficacy.90 Dry gas-vaporised H2O2 (8 g peroxide/m3) resulted in killing of 96.6–100% C. auris isolates in another report, although strain resistance varied significantly.88

Hand hygiene
Optimal HCW hand hygiene practices are considered important for outbreak control and for units caring for patients with C. auris.77,80 An in vitro study demonstrated that 2% chlorhexidine gluconate in 70% isopropyl alcohol for 2 min caused >5 log10 reduction in various clades of C. auris and was superior to 2% chlorhexidine gluconate alone.87 Alcohol-based hand rubs are recommended when hands are not visibly soiled.77,91 If hands are visibly soiled, washing with soap and water is recommended.77,91 Gloves are not a substitute for hand hygiene.

Decolonisation
In vitro data suggest C. auris is susceptible to chlorhexidine,75,88 but persistent colonisation is described despite daily chlorhexidine bathing.19,59,76 Routine patient decolonisation cannot be definitively recommended but may be considered in settings where transmission persists despite other interventions.39

Screening/surveillance
Patient populations requiring screening
Screening of close contacts (defined in ‘Pre-emptive isolation’ above) for C. auris colonisation is necessary to prevent transmission since the time from initial exposure to colonisation can be as short as 4 h.19 Other potential contacts include patients who overlapped on a ward with a patient with C. auris and patients who have occupied a room recently vacated by a patient with C. auris, especially if cleaning practices were suboptimal.80 Patients should be screened if transferred directly from an overseas healthcare facility or managed in an overseas healthcare facility (minimum of an overnight stay) during the previous 12 months.

During outbreaks, screening the hands of HCW on affected wards failed to identify culture-positive HCW.19,21 One study identified transient colonisation of the nares in 1 of 258 HCW, without evidence of transmission.19 Therefore, HCW screening should only be considered if epidemiological investigations suggest HCW are a likely source or where ongoing transmission is identified despite adherence to other interventions.

Contamination of affected patients’ rooms is common,21,83 but environmental sampling is generally not recommended.77 However, it may be considered if epidemiologic evidence links specific environmental sources to transmission or where transmission persists despite other interventions.
Surveillance strategies

Index cases of *C. auris* should prompt screening of close contacts. In facilities with >1 patient with *C. auris*, screening activities should be broadened as follows:

- Initially, screening of ward contacts is recommended.
- Point-prevalence surveys of an entire ward or facility may also be required to assess the extent of transmission and to identify all colonised patients.80,81
- Repeated screening of currently hospitalised patients (e.g. weekly screening)19 should be considered if further cases are identified despite other measures.

Screening sites

*C. auris* colonises skin of both symptomatic and asymptomatic patients.18 Of various body sites, axillary and inguinal swabs are most frequently positive.77,80,83 Therefore, composite swabs of the axilla and groin should be obtained as a minimum. However, in some published outbreak responses, specimens of urine, stool, drain fluids and other non-sterile sites, including the nares, vagina, rectum, wounds, vascular line/exit sites and other sites have yielded *C. auris*.19,21,22,32,80 In one study, adding nasal swabs to composite axilla/groin swabs yielded 10.4% (36/346) positive cultures. Of these, 14 (38.9%) were positive on composite axilla/groin swabs plus nasal cultures, 13 (36.1%) were positive on axilla/groin composite swabs alone and only 9 (25%) were positive on nasal cultures alone.22 Data from colonised patients show that a single negative screen does not reliably exclude carriage, but reliability increases with an increasing number of negative swabs.20

Other control measures

Notification to relevant jurisdictional public health departments may be required to assist with coordinated responses. Patients with *C. auris* should have an alert in their medical records that ensures appropriate isolation measures are taken at re-admission. There is no provision to clear a patient of *C. auris*-positive status. At patient transfer to another healthcare facility, the receiving facility must also be notified of the patient’s status and required infection control precautions.80 Healthcare facilities where *C. auris* is identified should ensure appropriate management of indwelling devices, including clinical governance systems with authority to mandate effective care-bundles, and HCW adherence to multimodal infection prevention strategies.17,61 Effective local antifungal stewardship programs also need to be implemented.

Refer to Box 3 for a summary of infection prevention and control recommendations.

### Box 3 Summary of infection prevention and control recommendations

R15. All patients colonised or infected with *Candida auris* should be placed in a single room (with dedicated bathroom or commode or fans) and managed using Standard and Contact Precautions for the entire hospital stay and all subsequent hospital admissions.

R16. Consider cohorting patients infected or colonised with *C. auris* if single rooms are unavailable.

R17. Single-patient use or single-use equipment should be used wherever possible.

R18. If a patient needs to leave their room to go to another department, the receiving department should be notified of the patient’s *C. auris* status and advised regarding necessary precautions.

R19. High-risk patients undergoing screening should be preemptively placed in a single room and managed using Standard and Contact Precautions until screening results are available.

R20. Close contacts of a *C. auris* patient (i.e. current room contacts and room contacts within the prior month (including at other wards/facilities)) can be de-isolated after three consecutive negative screens at least 24 h apart. All other persons undergoing screening can be de-isolated after a single negative screen.

R21. All cleaning should be performed using both detergent and disinfectant as per the manufacturer’s instructions, particularly with respect to contact time. Products that claim to have sporicidal activity should be used for disinfection (e.g. ≥1000 ppm bleach, peracetic acid or accelerated hydrogen peroxide). Quaternary ammonium compounds are not reliably effective against *C. auris* and should not be used. Non-touch disinfection techniques (e.g. UV-C light, hydrogen peroxide vapour) may be used as an adjunct, but should not replace the use of a sporicidal chemical agents, and must be preceded by environmental cleaning.

R22. Patient rooms should be cleaned and disinfected at least once daily. A thorough terminal clean should occur once the patient is discharged from the room. Fabric and disposable curtains should be changed at this time.

R23. Shared patient equipment should be cleaned and disinfected between patients, ideally with a sporicidal agent (subject to equipment compatibility).

R24. Healthcare workers caring for patients with *C. auris* should use alcohol-based hand rubs when hands are not visibly soiled. If hands are visibly soiled, washing with soap and water is recommended.

R25. No recommendation can be made about decolonising patients with *C. auris* using chlorhexidine body washes.

R26. Upon identification of a single case of *C. auris*, all close contacts should be screened for colonisation.

R27. Patients admitted to a healthcare facility who have had at least an overnight stay in an overseas healthcare facility in the past 12 months should be screened for *C. auris*. 

Diagnosis, management and prevention of *Candida auris*
R28. Upon identification of >1 patient with C. auris at a single healthcare facility, ward contacts should be screened. Point-prevalence screening of the affected ward and repeated screening (e.g. weekly screening of currently hospitalised patients) should be considered if there is ongoing transmission despite other measures.

R29. Composite axilla and groin swabs (as a minimum) are recommended for screening purposes. To enhance yield, screening specimens may also be collected from vascular line exit sites, wounds, drain tube output and urine.

R30. Screening of healthcare workers and the environment is not routinely recommended, but may be considered if strongly implicated in transmission by epidemiologic evidence or in situations where ongoing transmission is identified despite adherence to recommended interventions.

R31. Patients with C. auris should have an alert placed in their medical record. On transfer to another healthcare facility, the receiving facility must be provided with notification of the patient’s C. auris status and recommended infection control precautions.

Conclusion

*C. auris* is an emerging multi-drug resistant yeast that has caused significant nosocomial outbreaks overseas. Reliable laboratory identification, appropriate therapy to reduce impact on patient outcomes and timely institution of infection control measures are necessary to control outbreaks.

Acknowledgements

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Association between socioeconomic status and incident atrial fibrillation

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Key words atrial fibrillation, screening, socioeconomic status.

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Abstract

Background: Low socioeconomic status is associated with cardiovascular diseases, and an association with atrial fibrillation (AF) could guide screening.
Aim: To investigate if indices of advantage/disadvantage (IAD), index of education/occupation (IEO) and index of economic resources were associated with incident AF, independent of risk factors and cardiac function.
Methods: We studied community-based participants aged ≥65 years with AF risk factors (n = 379, age 70±4 years, 45% men). The CHARGE-AF score (a well validated AF risk score) was used to assess 5-year risk of developing AF. Participants also had baseline echocardiograms. IAD, IEO and index of economic resources were obtained from the 2011 Socio-Economic Indexes for Areas score, in which higher decile ranks indicate more advantaged areas. Patients were followed up for incident AF (median 21 (range 5–31) months), with AF diagnosed by clinical review, including 12-lead electrocardiogram (ECG), as well as single-lead portable ECG monitoring used to record 60 s ECG tracings five times/day for 1 week. Cox proportional hazards models were used to assess the association between socioeconomic status and incident AF.
Results: Subjects with AF (n = 50, 13%) were more likely to be male (64 vs 42%, P = 0.003) and had higher CHARGE-AF score (median 7.1% (5.2–12.8%) vs 5.3% (3.3–8.6%), P < 0.001). Areas with lower socioeconomic status (IAD and IEO) had a higher risk of incident AF independent of LV function and CHARGE-AF score (hazard ratio for IAD 1.16, 95% confidence interval 1.05–1.29, P = 0.005 and hazard ratio for IEO 1.18, 95% confidence interval 1.07–1.30, P = 0.001).
Conclusion: Regional socioeconomic status is associated with risk of incident AF, independent of LV function and clinical risk. This association might permit better regional targeting of prevention.

Introduction

Atrial fibrillation (AF) is associated with stroke, heart failure, increased all-cause mortality1,2 and substantial financial cost.3,4 The epidemics of obesity, diabetes mellitus and metabolic syndrome have been associated with the increasing prevalence of AF, which has become a significant population health problem.5–7 The early diagnosis of AF may lead to individualised lifestyle intervention8 and anticoagulation, and these steps may be associated with a reduction in complications and healthcare costs. The development of hand-held electrocardiogram (ECG) screening devices,9–15 has increased the feasibility of AF screening. Appropriate selection of patients for screening is of critical importance; the
development of a risk assessment score,\textsuperscript{16,17} based on the link between AF and clinical risk factors, is an important component of identifying individual patients at risk. The introduction of a screening programme should also involve consideration of which communities are at risk.

Socioeconomic deprivation is strongly associated with increased risk of metabolic syndrome and coronary artery disease,\textsuperscript{18–20} beyond its association with reduced healthcare access. Low household income influences dietary choices, psychological well-being and is associated with a sedentary lifestyle.\textsuperscript{21} Poor literacy and education levels may affect treatment adherence and risk awareness. There may also be higher rates of substance and alcohol abuse in deprived areas.\textsuperscript{22} However, the association between socioeconomic deprivation and AF risk is controversial, with reports of an association of lower household income with increased AF risk,\textsuperscript{23} balanced by other evidence that neighbourhood deprivation and socioeconomic disparities were not independently associated with AF.\textsuperscript{24} The purpose of this study was to assess the association of regions of socioeconomic deprivation with risk of incident AF.

Methods

Study population

This prospective observational cohort study recruited participants from both urban and rural settings in Tasmania (an island located south of the Australian mainland) and Victoria (a larger State in the south of mainland Australia). Apart from the major cities (Hobart and Launceston), much of Tasmania is geographically isolated, with limited access to healthcare.\textsuperscript{25} Participants from the community ≥65 years were recruited if they had one or more AF/heart failure (HF) risk factors, including hypertension (systolic blood pressure (BP) ≥140 mmHg or preexisting use of antihypertensive medications), type 2 diabetes mellitus (T2DM, based on self-report of diagnosis or the current use of diabetic medications) and obesity (body mass index ≥30). Subjects were excluded if they were unable to provide written consent, had known HF or left ventricular (LV) systolic dysfunction, moderate/severe valvular disease or life expectancy <1 year. All patients with a history of AF and anticoagulation or were noted to have AF during baseline 12-lead ECG and echocardiograms were excluded. All patients were provided written informed consent and the study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki and approval was obtained from the Tasmanian Human Research Ethics Committee (HREC project number H0013333). The study was registered on the Australian and New Zealand clinical trials registry (ACTRN1261400080628).

Clinical findings

Participants provided a clinical history and answered questionnaires to assess overall health status at the start of the study. Information regarding demographics, past medical history, medication history and baseline examination data (height, weight, body mass index, BP) was recorded for all participants. Baseline 12-lead ECG and echocardiography were conducted in all participants, and patients with previously unrecognised HF were excluded. Assessment of AF risk was performed using the CHARGE-AF score.\textsuperscript{17} Exercise capacity was assessed using the 6-minute walk test.

Assessment of socioeconomic status

All participants had information collected on education level. The Socio-Economic Indexes for Areas (SEIFA) score is derived from several domains of national census data (including education, housing, household income, employment and occupation) to provide a multidimensional assessment of socioeconomic status based on postcode. This was used to describe the regional variations of participants’ overall socioeconomic status.\textsuperscript{25}

The SEIFA score has three main indices: an index of advantage/disadvantage (IAD, based on income, occupation and housing), an index of education/occupation (IEO, based on education and occupation) and an index of economic resources (IER, based on individual income, mortgage repayments, rental return and family income). These indices are expressed to deciles, with the lowest scoring 10% of areas given a decile number of 1 and the highest 10% of areas are given a decile number of 10. Hence, higher scores reflect more advantaged areas.\textsuperscript{25}

AF follow up

AF was diagnosed using multiple detection methods. All participants had baseline and follow-up assessment, including a 12-lead ECG and echocardiogram. In the interim, any patients diagnosed with AF by local physicians were documented. Screening for subclinical AF was performed using a single-lead ECG device (Remon RM-100; Semacare, Shenzhen, China). The single-lead device was used to record 60-s single-lead ECG tracings using three points of finger contact with electrodes, five times per day for 1 week (i.e. 35 recordings). ECG recordings were then exported as PDF files for interpretation, and all were assessed by a physician. The presence of AF (an irregular rhythm of ≥30 s with a variable R-R interval and absent P waves) was confirmed by two
independent physicians who were blinded to the patient’s clinical details. The patient was advised of the recognition of subclinical AF, and further management and investigation was provided by their usual medical practitioner.

**Outcome measures**

Our primary outcome measure was the overall proportion of the cohort with new onset AF during the follow-up period.

**Statistical analysis**

All categorical variables are presented as frequencies/percentages, and continuous variables presented as means/standard deviation (if normally distributed) or medians/interquartile range (if nonparametric). Patients with incident AF were compared with those remaining in sinus rhythm. Groups were compared using the Chi-squared test for categorical data and the independent two sample t-test for continuous data. Patients were grouped according to the SEIFA rank (<5 vs ≥5) and Nelson–Aalen cumulative hazard estimate plots were constructed, and the log-rank test used to assess the differences between curves. A Cox proportional hazards regression analysis was used to calculate the adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the association between each socioeconomic index and incident AF. Clinically relevant model covariates included CHARGE-AF score, global longitudinal strain, gender and indexed left atrial volume. The follow-up time was the time from the initial baseline clinical assessment to the completion of portable device screening or the date of diagnosis of AF (whichever came first). Analyses were considered to be statistically significant if two-tailed $P$ values were <0.05. Statistical analysis was performed using spss v.22 (SPSS, Chicago, IL, USA) and Stata v.13 (StataCorp, College Station, TX, USA).

**Results**

**Patient characteristics**

The baseline characteristics of the 379 subjects included in the study (mean age 70 ± 4 years, 45% male) are summarised in Table 1. Thirteen participants (3%) had a previous diagnosis of paroxysmal AF. Cardiovascular risk factors (including T2DM, obesity, hypercholesterolaemia and hypertension) were highly prevalent. There was a large proportion of participants with low education levels (43% had not completed high school and approximately three in four had not completed university education). Most participants were recruited from areas with socioeconomic deprivation (median IAD 5 ± 6, median IEO 5 ± 6 and median IER 4 ± 5).

**AF during follow up**

Over a median follow up of 21 months (range 5–31 months), 50 patients (13%) were diagnosed with AF. Of these, 37 patients (9.8%) were diagnosed with incident AF, 23 of whom (6%) were diagnosed with portable ECG monitoring while 14 (4%) were diagnosed by local physicians during the follow-up period or had AF during hospitalisations. Table 2 compares the characteristics of those with AF and sinus rhythm; new onset AF was more likely in men, and in those with a higher CHARGE-AF score and those from socioeconomically deprived areas ($P < 0.05$).

<table>
<thead>
<tr>
<th>Demographics</th>
<th>$n = 379$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD) (years)</td>
<td>70.3 (4.2)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>169 (45)</td>
</tr>
<tr>
<td>Systolic BP (SD) (mmHg)</td>
<td>140.6 (15.9)</td>
</tr>
<tr>
<td>Diastolic BP (SD) (mmHg)</td>
<td>82.5 (9.9)</td>
</tr>
<tr>
<td>Heart rate (SD) (b.p.m.)</td>
<td>68.7 (10.8)</td>
</tr>
<tr>
<td>BMI (SD) (kg/m²)</td>
<td>29.8 (5.2)</td>
</tr>
<tr>
<td>Current/previous smoking, n (%)</td>
<td>182 (48)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>176 (46)</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>176 (46)</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>205 (54)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>293 (77)</td>
</tr>
<tr>
<td>Previous history of IHD, n (%)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Previous history of AF, n (%)</td>
<td>13 (3)</td>
</tr>
<tr>
<td>Previous chemotherapy, n (%)</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Median 6-min walk test (IQR) (m)</td>
<td>504 (96)</td>
</tr>
<tr>
<td>Median CHARGE-AF (IQR) (%)</td>
<td>6.8 (6.6)</td>
</tr>
<tr>
<td>Median CHA₂DS²-VASC (IQR) (%)</td>
<td>3.0 (2.0)</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Ejection fraction (SD) (%)</td>
<td>62.8 (6.2)</td>
</tr>
<tr>
<td>Global longitudinal strain (SD) (%)</td>
<td>−18.8 (2.5)</td>
</tr>
<tr>
<td>E/e’ (average of lateral and septal) (SD)</td>
<td>8.7 (2.5)</td>
</tr>
<tr>
<td>Left atrial volume, indexed (SD) (mL/m²)</td>
<td>31.5 (9.1)</td>
</tr>
<tr>
<td>Left ventricular mass, indexed (SD) (g/m²)</td>
<td>88.8 (21.7)</td>
</tr>
<tr>
<td>Social factors</td>
<td></td>
</tr>
<tr>
<td>Median SEIFA Index of Advantage/Disadvantage (IQR)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Median SEIFA Index of Education/Occupation (IQR)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Median SEIFA Index of Economic Resources (IQR)</td>
<td>4 (5.0)</td>
</tr>
<tr>
<td>Completed high school, n (%)</td>
<td>214/375 (57)</td>
</tr>
<tr>
<td>Completed university, n (%)</td>
<td>88/376 (23)</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; IHD, ischaemic heart disease; IQR, interquartile range; SEIFA, Socio-Economic Indexes for Areas.
**Association between socioeconomic status and AF risk**

SEIFA data were available in 370/379 participants (with 48 AF outcomes). Table 3 summarises the features associated with AF risk, including increased age, male gender, reduced global longitudinal strain, increased left atrial volume and socioeconomic deprivation. Those who developed AF had lower median SEIFA indices than those in sinus rhythm (IAD (4.0 (range 2–6) vs 5.0 (range 3–8), P = 0.005), IER (4.0 (range 2–5) vs 5.0 (range 3–8), P = 0.002) and IEO (3.5 (range 2–7) vs 6.5 (range 2–8), P = 0.02)). There were no differences in AF rates noted in participants with high school or tertiary level education. In a multivariable model, adjusted for gender, clinical risk factors, LV function and left atrial volume, increased incident AF risk was associated with disadvantaged areas (HR for IAD = 1.16, 95% CI 1.05–1.29, P = 0.005) and areas with lower education/occupation levels (HR for IEO = 1.18, 95% CI 1.07–1.30, P = 0.001) (Fig. 1, Table 3). Areas with lower economic resources were not independently associated with increased incident AF risk (HR for IER = 1.11, 95% CI 0.99–1.24, P = 0.08).

**Table 2** Comparison of baseline characteristics between patients with AF and sinus rhythm

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Atrial fibrillation n = 50</th>
<th>Sinus rhythm n = 329</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD) (years)</td>
<td>71.3 (5.0)</td>
<td>70.1 (4.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>32 (64)</td>
<td>137 (42)</td>
<td>0.003</td>
</tr>
<tr>
<td>Systolic BP (SD) (mmHg)</td>
<td>135.5 (18.3)</td>
<td>141.4 (15.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic BP (SD) (mmHg)</td>
<td>82.6 (11.2)</td>
<td>82.5 (7.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>BMI (SD) (kg/m²)</td>
<td>29.3 (4.7)</td>
<td>29.9 (5.3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Current/previous smoking, n (%)</td>
<td>24 (48)</td>
<td>158 (48)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>27 (54)</td>
<td>149 (45)</td>
<td>0.25</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>19 (38)</td>
<td>157 (48)</td>
<td>0.419</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>25/47 (53)</td>
<td>180/321 (56)</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>38 (76)</td>
<td>255 (78)</td>
<td>0.81</td>
</tr>
<tr>
<td>Previous history of IHD, n (%)</td>
<td>5 (10)</td>
<td>11 (3.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Median CHARGE-AF (IQR) (IQR)</td>
<td>7.1 (7.6)</td>
<td>5.3 (5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median CHA²DS²-VASC (IQR)</td>
<td>3.0 (2.0)</td>
<td>3.0 (2.0)</td>
<td>0.93</td>
</tr>
<tr>
<td>Functional capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six-min walk test (SD) (m)</td>
<td>498 (102)</td>
<td>508 (98)</td>
<td>0.50</td>
</tr>
<tr>
<td>Social factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median SEIFA Index of Advantage/Disadvantage (IQR)</td>
<td>4 (4.0)</td>
<td>5.0 (5.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Median SEIFA Index of Education/Occupation (IQR)</td>
<td>3.5 (5.0)</td>
<td>6.0 (5.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median SEIFA Index of Economic Resources (IQR)</td>
<td>4.0 (3.0)</td>
<td>5.0 (5.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Completed high school, n (%)</td>
<td>28 (54)</td>
<td>186/325 (57)</td>
<td>0.87</td>
</tr>
<tr>
<td>Completed university, n (%)</td>
<td>8 (16)</td>
<td>80/326 (25)</td>
<td>0.18</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (SD) (%)</td>
<td>60.7 (7.2)</td>
<td>63.2 (5.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Global longitudinal strain (SD) (%)</td>
<td>−17.7 (3.3)</td>
<td>−19.0 (2.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>E/e’ (average of lateral and septal) (SD)</td>
<td>8.6 (2.7)</td>
<td>8.8 (2.5)</td>
<td>0.67</td>
</tr>
<tr>
<td>Left atrial volume, indexed (SD) (mL/m²)</td>
<td>34.0 (10.3)</td>
<td>31.1 (8.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Left ventricular mass, indexed (SD) (g/m²)</td>
<td>93.6 (23.3)</td>
<td>87.8 (21.3)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; IHD, ischaemic heart disease; IQR, interquartile range; SEIFA, Socio-Economic Indexes for Areas.

**Discussion**

The results of our study suggest that a significant number of elderly people in the community with risk factors have subclinical AF. Regional socioeconomic deprivation is associated with AF independent of other clinical risk factors and cardiac function. Areas with higher household income, higher rates of education and employment were associated with reduced risk of incident AF.

**Socioeconomic status and AF**

Socioeconomic deprivation is well established as a risk factor for metabolic syndrome and cardiovascular disease, but the association between socioeconomic status and AF is less clear. A large Swedish study did not find an independent association between socioeconomic status and hospitalised AF, although an association was found in women. The ARIC cohort found that low family income was associated with increased risk of AF, with lower education levels associated with increased AF risk in women. After adjusting for confounders, we found that regional indices of lower
income/education were associated with AF in both sexes. The use of regional indices of socioeconomic status provides a basis of using geographic location in planning screening, in a way that using individual income or educational data would be inaccessible.

There may be several mechanisms by which socioeconomic status can affect AF risk and management. AF has been strongly associated with metabolic syndrome and obesity, both of which are strongly influenced by socioeconomic status. Household income and education levels influence dietary habits and physical activity levels. Interestingly, in our study despite high rates of obesity, T2DM and hypertension at baseline, we did not see any significant difference in these markers in participants with AF compared with those in sinus rhythm. It is possible that this could be due to our small sample size and limited follow up. These markers are components of the CHARGE-AF score, where we did note a higher score in those with AF compared with those in sinus rhythm. It is possible that even though the overall rates between both groups were similar, those who developed AF may have poorly controlled risk factors or may have individuals with multiple risk factors present, hence creating incremental risk. Children born to parents of low socioeconomic status have higher risk of low birth weight which has been shown to be associated with AF risk. The higher rates of alcohol and substance abuse in areas of socioeconomic deprivation are both associated with AF risk. There may be added challenges such as poor health awareness in this cohort and issues relating to poor adherence, as limited household income may influence decisions made on anticoagulation and other pharmacological therapy. Irrespective of the mechanisms involved, socioeconomic status appears to be associated with AF and in our study, it was as important a risk factor as left atrial volume and LV function.

### Early diagnosis of AF and community screening

AF creates a significant burden on both patients and the healthcare system. For patients, it is associated with increased risk of stroke and HF as well as causing symptoms and impaired quality of life. AF seems likely to continue to increase in incidence and the costs to the healthcare system will continue to increase. Early diagnosis might be achieved by community screening programmes, but successful AF screening requires both an appropriate diagnostic tool as well as careful selection of the at-risk population.

The incident AF rate of 9.8% in this study – higher than previously reported in the literature – is attributable to not only age and clinical risk factors for AF, but also social vulnerability. Elderly, socially isolated patients with poor access to affordable healthcare, limited household income and poor education levels are often encountered in hospital following the complications of AF. Early diagnosis offers the possibility for early initiation of treatment which may offset...
some of the complications which may lead to reduced hospitalisations and associated healthcare costs. Patients with subclinical AF and atrial tachyarrhythmias have an increased risk of stroke and cardiovascular events similar to those with established AF, and anticoagulation may help reduce the incidence of stroke in this cohort. Active lifestyle intervention may lead to a reduction in symptom burden and in the need for repeat ablation procedures and an improvement in quality of life. Initiation of lifestyle intervention and risk factor modification following early diagnosis of AF may be associated with positive LA remodelling, which may reduce disease progression and produce additional health benefits, including reduction in cardiovascular risk and improvement in exercise capacity.

**Clinical implications**

The results of our study have several important clinical implications. We have demonstrated a significant burden of subclinical AF in elderly people with risk factors. We have also demonstrated that AF screening using portable ECG monitoring is feasible. The finding that low regional socioeconomic status is associated with increased AF risk has important implications for mass screening. Screening programmes conducted in these areas will likely yield higher detection rates, improving cost-effectiveness and providing access to early intervention programmes to those at the highest risk of complications and hospitalisations.

**Limitations**

There are several limitations of our study. There is a potential for population selection bias as participants were recruited with newspaper and radio advertising. Selection bias may influence the rates of clinically diagnosed AF in the cohort. Patients from areas of high socioeconomic status who may have better access to healthcare and improved health literacy may present...
more frequently for review, potentially resulting in higher rates of clinically diagnosed AF. Our patient sample was small, and we had a limited number of AF outcomes. Our patient population was predominately white Australian, and our results are not generalisable to the indigenous population or other ethnicities. Our screening for subclinical AF was done for a 1-week period of intermittent ECG monitoring, and it is possible that resulted in some AF outcomes to be potentially missed. Our study focused on the assessment of regional socioeconomic status as we investigated the implications to a community AF screening programme. Hence, the results of our study cannot be used for individual risk assessment. Our cohort study is unable to establish causality. Intervention studies are required in the future to determine if socioeconomic deprivation is a risk factor for AF and if community-based interventions can result in reduced AF incidence.

**Conclusion**

Elderly patients with risk factors have a high prevalence of subclinical AF, especially in regions of socioeconomic deprivation. The finding that socioeconomic deprivation is independently associated with incident AF suggests that additional resources and access to healthcare are needed in selected communities to improve health outcomes.

**References**

22. Fone DL, Farewell DM, White J, Lyons RA, Dunstan FD. Socioeconomic patterning of excess alcohol consumption and binge drinking: a


Resource use and outcomes in patients with dialysis-dependent chronic kidney disease admitted to intensive care

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Key words
critical illness, critical care, chronic renal insufficiency, renal dialysis, outcome assessment, intensive care unit.

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Abstract

Background: Central Australia (CA) has a high prevalence of haemodialysis-dependent chronic kidney disease (CKD5D). CKD5D is associated with an increased need for critical care services.

Aims: To describe the demographic features, critical care resource use and outcomes of patients with CKD5D requiring intensive care admission in CA.

Methods: Retrospective matched cohort database study. Patients with CKD5D who required admission for critical illness between 1 July 2015 and 30 June 2016 were identified using the Centre for Outcome and Resource Evaluation Outcome Measurement and Evaluation Tool (CORE COMET) and matched with patients without CKD5D. The primary outcome was all cause mortality. Secondary outcomes explored use of critical care and other ongoing healthcare use.

Results: There were 621 critical care admissions during the study period. Of these, CKD5D patients comprised 88 admissions (14%), representing 63 patients. Compared to matched controls, these patients had a similar mortality at a median follow up of 463 days (17% vs 22%, \( P = 0.50 \)) which did not change when patients with an intensive care unit length of stay (ICU LoS) less than 4 days were excluded. CKD5D patients had a shorter median ICU LoS (1.3 vs 2.9). Although those with CKD5D had higher healthcare resource use, the rate of utilisation remained unchanged by their ICU admission.

Conclusions: This retrospective observational matched cohort study examining the burden of disease amongst CKD5D patients in CA suggests that there is no additional mortality burden in this group, nor do they require significantly higher critical care resources compared to a matched cohort.

Introduction

Dialysis-dependent chronic kidney disease (CKD5D) is associated with significant morbidity and mortality, and prevalence is increasing both within Australia and internationally at unprecedented rates.\(^1\)–\(^6\) In 2016 there were 12 706 patients requiring maintenance haemodialysis in Australia, an increase of approximately 30% over the preceding decade.\(^5\)

In no other jurisdiction is this increase as conspicuous as in the Northern Territory (NT). Prevalence is increasing at around 5.5% annually (20% higher than the national average) and the rising demand for dialysis is placing additional strain on the healthcare system.\(^7\) Newly diagnosed patients are more likely to be Aboriginal or Torres Strait Islander (indigenous) and commence dialysis at a younger age (50 vs 62 years).\(^7,8\)

Alice Springs Hospital (ASH) provides secondary healthcare to Central Australia (CA) where this increase is most marked. ASH services a catchment area that contains approximately 50 000 people. There are currently 380 dialysis-dependent patients (a prevalence of 7168 per million), approximately 15-fold the national prevalence.\(^5,9\)

Patients with CKD5D have a higher chance of requiring intensive care support during critical illness.\(^1\)–\(^3,10\)\(^12\)

This is perhaps due to complex pre-existing co-morbidity and physiological fragility. Irrespective of the causes it is likely that as the prevalence of CKD5D increases, the need for critical care will predictably escalate.\(^6,13\)
While there is some evidence to assist clinicians in providing services to this population, most studies did not include Indigenous Australian patients. A recent systematic review including 16 studies investigating the epidemiology of patients with CKD5D requiring intensive care reported in-hospital mortality varied between 8.8% and 56%. The two Australian papers included in this meta-analysis did not identify Indigenous Australians in their study samples. Given the unique demographic features that characterise the CKD5D population in CA (who are predominantly indigenous, comparatively younger and with high rates of diabetic nephropathy), it is possible the inferences from these studies may not be applicable.

This study aims to describe the epidemiology of CKD5D patients requiring critical care, to examine the resource utilisation of this group in intensive care and to report on the medium-term mortality.

Methods

This was a retrospective matched cohort study conducted in the intensive care unit (ICU) of the ASH. This is a 10-bed unit with approximately 600 admissions per year. It is the only critical care facility servicing a catchment area exceeding 1.5 million square kilometres in CA (Fig. 1). Ethical approval was granted by the Central Australian Human Research Ethics Committee (CA-18-3030).

Patients with CKD5D admitted to the ICU between 1 July 2015 and 30 June 2016 were identified within the ASH Centre for Outcome and Resource Evaluation Outcome Measurement and Evaluation Tool (CORE COMET) database. This database holds the demographic details, acute physiology, chronic disease states and limited resource utilisation information (such as ICU and hospital length of stay (LoS), need for mechanical ventilation and/or the need for vasopressor/inotropic support) for submission to the Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcome and Evaluation (CORE) Adult Patient Database (APD) – one of four clinical quality registries. Diagnostic codes and chronic disease state(s) are defined in the ANZICS CORE Data Dictionary. The database calculates the Acute Physiology And Chronic Health Evaluation (APACHEIII) score, and corresponding APACHEIII risk of death (RoD). In addition, the number of emergency department (ED) presentations and hospital admissions in the 12 months prior and the 12 months following the index ICU admission were collected from the Northern Territory Government’s (NTG) Clinical Work Station (CWS) in order to assess the impact of an ICU admission on persisting morbidity. Presentations solely for the purposes of maintenance haemodialysis or outpatient clinic appointments were not included.

Mortality at the census date (1 July 2017) was recorded by cross referencing with the NTG clinical work station (CWS) which records deaths across the NTG’s Health Network which covers approximately two-thirds of clinics within the catchment area. Remaining clinics notify the hospital of local deaths which are confirmed with the NTG department of births, deaths and marriages and the CWS details are then updated.

The admission of a patient with CKD5D who required critical care was matched in a 1:1 ratio with a patient admitted to the ASH ICU between 1 July 2014 and 30 June 2017 by age, ANZICS modified APACHEIII diagnostic category, APACHEIII score and sex. There is no diagnostic code for a critical care admission that results from missing a haemodialysis session(s). While rare in other jurisdictions, this is a relatively common presentation to both the ASH, and for those requiring critical care support (such as non-invasive ventilation for fluid overload, or continuous cardiac monitoring for hyperkalaemia induced rhythm disturbance), to the ICU. Because of the high proportion of these patients for which an equivalent code does not exist in the non-CKD5D population, these were matched with a similar diagnostic code such as non-cardiogenic pulmonary oedema.

Aims

The primary aim was to report the mortality of CKD5D patients requiring admission for a life threatening illness in CA at a minimum of 12 months after an index admission, compared to the mortality of a matched cohort. Secondary aims were to describe the resource use of this group, and to compare these against a matched cohort.

A priori determined subgroup analyses were conducted on patients who had an ICU LoS greater than 2 days, and greater than 4 days as a surrogate marker of illness acuity.

Statistical analysis

Data were analysed in Stata V15.1 (StataCorp Incorporated, TX, USA). Data are reported as mean (standard deviation) for normally distributed data, median (inter-quartile range) for non-normally distributed data or number (percentage) for categorical data. Normality was assessed for using the Shapiro–Wilks test. Univariate analyses using the Students t-test or the Kolmogorov–Smirnov test for parametric and non-parametric data respectively, and the χ2 test for categorical data was undertaken to compare admissions of patients with and without CKD5D. In order to adjust for multiple comparisons, results were considered significant at \( P < 0.01 \).
In order to avoid double counting for longitudinal outcomes (mortality, healthcare utilisation), analysis was undertaken after excluding multiple re-admissions. Given that resource utilisation (such as vasoressin/inotrope support, mechanical ventilation and LoS) is related to episode data rather than patient level data a secondary sensitivity analysis was planned using the original admission data.

**Results**

Between 1 July 2015 and 30 June 2016 there were 621 admissions to the ASH ICU (Fig. 2). Of these, 88 (14.2%) admissions, representing 63 (11.6%) patients, were correctly coded as having CKD5D, the vast majority of whom (98.4%) identified as indigenous (Table 1). All were receiving maintenance haemodialysis. Diabetic

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**Figure 1** Catchment area for Alice spring hospital (ASH) which extends from Kiwirrkura in the west, to Alpurrurrulam (Lake Nash) in the northeast, Newcastle waters in the north to Marla in the south.
nephropathy was the predominant aetiology of CKD (76% confirmed or likely) and CKD patients had a median duration of haemodialysis of 5 years.

Before pair-matching, CKD patients were older, but not significantly so, and were more likely to identify as indigenous ($\chi^2 = 35.6, P < 0.001$; Table 1). Chronic disease profile, as defined by the ANZICS CORE data dictionary, was similar with the exception of renal failure.14 CKD patients were significantly less likely to be admitted with a ‘trauma’ diagnosis, but more likely to be admitted with a ‘cardiovascular’ or ‘metabolic’, probably representing a missed dialysis session(s), diagnosis (Table 1). APACHE III scores were significantly higher and there was a correspondingly significantly higher APACHE III RoD score (Table 1). CKD patients were significantly less likely to require mechanical ventilation, but more likely to require vaso-active therapy. Despite the higher APACHE III score, ICU and hospital LoS, as well as mortality between the groups, were similar. There was a relatively high proportion of admissions (33%) that were for patients who had missed dialysis session(s) and who required critical care support, representing 15 patients (24% of the final CKD cohort).

All patients underwent matching by age, APACHE III diagnostic code, APACHE III score and sex with a cohort admitted to the ASH ICU from a similar time period (Supporting Information Table S1).

After multiple admissions were excluded 63 CKD patients and their matched controls underwent primary analysis (Table 2). Despite a statistically significant difference in the APACHE III score, there was no difference in the mean APACHE III RoD. For a similar illness acuity, CKD patients had a shorter ICU LoS (Kolmogorov–Smirnov = 0.35, $P = 0.001$). The pair matched cohort was more likely to have an ICU LoS greater than both 2 and 4 days (Table 2), perhaps reflecting the inability of the APACHE III scoring system to describe adequately the illness severity for CKD patients who have missed dialysis session(s) in particular. There were no significant differences in the critical care use required for each group measured by the requirement and duration of mechanical ventilation, vasoactive therapies or continuous renal replacement therapy (Table 2).

Significantly CKD patients had both more ED presentations and hospital admissions in the 12 months prior to their index ICU admission, and both the number of presentations and the number of admissions were also significantly higher (Table 2) culminating in significantly fewer hospital free days (HFD). This trend continued in the 12 months following the index admission, however, while there were fewer patients in the matched group requiring hospital re-admission, it was for a longer period of time resulting in no statistical difference in the HFD between the groups (337 vs 330 days, Kolmogorov–Smirnov = 0.17, $P = 0.29$) in the 12 months following the index ICU admission.

There were no significant differences in hospital destination, nor a significant difference in hospital mortality (Table 2). Although the CKD cohort had a significantly longer duration of follow up from index admission to the census date, there was no difference in long-term mortality (22% vs 17.4%, $\chi^2 = 0.45, P = 0.5$). Figure 3 demonstrates the Kaplan–Meier curves for the two groups.

Subgroup outcome analysis examining mortality in each group for those who required an ICU LoS of greater than 2 and 4 days showed no increase in mortality as ICU LoS increased (Table 3).

Secondary sensitivity analyses using admission data showed no significant difference from the data from individual patients (Table S1).

Discussion

Our retrospective matched cohort study of this unique demographic entity demonstrates a relatively high use of healthcare use, but a mortality that is comparable to a
cohort matched for illness severity at a median follow-up period of 463 days. Similarly, there was no significant difference in critical care resource use with similar rates of vasoactive therapy and CRRT, indeed, arguably this group required fewer resources with lower rates of mechanical ventilation and a shorter ICU LoS. Furthermore, in the CKD5D cohort an index admission to ICU did not result in an increase in healthcare use (measured

### Table 1 Pre-match comparison table comparing CKD5D with non-CKD5D patients admitted to ICU

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-CKD5D (n = 482)</th>
<th>CKD5D (n = 63)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at admission</td>
<td>48.2 (17.8)</td>
<td>52.7 (12.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Male</td>
<td>254 (52.7)</td>
<td>27 (42.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Indigenous</td>
<td>290 (60.1)</td>
<td>62 (98.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic disease burden†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukaemia</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>11 (2.3)</td>
<td>1 (1.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>8 (1.7)</td>
<td>0 (0.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>6 (1.2)</td>
<td>0 (0.0)</td>
<td>0.37</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>18 (3.7)</td>
<td>2 (3.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>18 (3.7)</td>
<td>2 (3.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Other chronic disease</td>
<td>5 (1.0)</td>
<td>0 (0.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>CKD5D aetiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>–</td>
<td>43 (68.3)</td>
<td>n/a</td>
</tr>
<tr>
<td>Chronic GN</td>
<td>–</td>
<td>6 (9.5)</td>
<td>n/a</td>
</tr>
<tr>
<td>Interstitial disease</td>
<td>–</td>
<td>2 (3.2)</td>
<td>n/a</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>–</td>
<td>1 (1.6)</td>
<td>n/a</td>
</tr>
<tr>
<td>Unknown (likely DN)</td>
<td>–</td>
<td>5 (7.9)</td>
<td>n/a</td>
</tr>
<tr>
<td>Unknown</td>
<td>–</td>
<td>6 (9.5)</td>
<td>n/a</td>
</tr>
<tr>
<td>Haemodialysis duration (years)</td>
<td>–</td>
<td>5 (3.6–8.3)</td>
<td>n/a</td>
</tr>
<tr>
<td>Type of admission†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDU</td>
<td>292 (63.3)</td>
<td>48 (76.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>ICU</td>
<td>169 (36.7)</td>
<td>15 (23.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Admission diagnostic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>51 (10.6)</td>
<td>14 (22.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Respiratory</td>
<td>79 (16.4)</td>
<td>6 (9.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>56 (11.6)</td>
<td>9 (14.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Neurological</td>
<td>40 (8.3)</td>
<td>4 (6.3)</td>
<td>0.80</td>
</tr>
<tr>
<td>Sepsis</td>
<td>118 (24.5)</td>
<td>14 (22.2)</td>
<td>0.76</td>
</tr>
<tr>
<td>Trauma</td>
<td>50 (10.4)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metabolic</td>
<td>39 (8.1)</td>
<td>15 (23.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MSS/skin/orthopaedic</td>
<td>27 (5.6)</td>
<td>1 (1.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>Missed haemodialysis</td>
<td>–</td>
<td>15 (23.8)</td>
<td>n/a</td>
</tr>
<tr>
<td>APACHEIII</td>
<td>38 (27–54)</td>
<td>61 (54–71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHEIII RoD</td>
<td>0.08 (0.11)</td>
<td>0.19 (0.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU LoS (days)</td>
<td>2.1 (1.1–4.3)</td>
<td>1.3 (0.67–2.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital LoS (days)</td>
<td>6.9 (3.5–12.9)</td>
<td>5.8 (2.5–11.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Mechanically ventilated</td>
<td>118 (24.5)</td>
<td>5 (7.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Vasoactive therapy‡</td>
<td>121 (25.1)</td>
<td>21 (33.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>CRRT</td>
<td>9 (1.2)</td>
<td>5 (7.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Discharge location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>376 (78.0)</td>
<td>52 (82.5)</td>
<td>0.51</td>
</tr>
<tr>
<td>IHT (other ICU)</td>
<td>32 (6.6)</td>
<td>0 (0.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>IHT (other hospital ward)</td>
<td>54 (11.2)</td>
<td>7 (11.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Nursing home</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>ICU death</td>
<td>10 (2.0)</td>
<td>2 (3.2)</td>
<td>0.64</td>
</tr>
<tr>
<td>Hospital death</td>
<td>19 (3.9)</td>
<td>4 (6.4)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

†Defined by Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Outcome and Measurement Evaluation Tool (ANZICS CORE COMET) data dictionary. ‡Inotrope and/or vasopressor requirement. APACHE, Acute Physiology And Chronic Health Evaluation; CKD5D, haemodialysis-dependent chronic kidney disease; CRRT, continuous renal replacement therapy; DN, diabetic nephropathy; GN, glomerular nephritis; ICU, intensive care unit; IHT, interhospital transfer; LoS, length of stay; MSS, musculoskeletal; RoD, risk of death.
<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Matched cohort</th>
<th>CKD5D</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 126)</td>
<td>(n = 63)</td>
<td>(n = 63)</td>
<td></td>
</tr>
<tr>
<td>Age at admission</td>
<td>52.7 (13.5)</td>
<td>52.7 (14.4)</td>
<td>52.7 (12.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>Male</td>
<td>54 (42.9)</td>
<td>27 (42.9)</td>
<td>27 (42.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Indigenous</td>
<td>104 (82.5)</td>
<td>42 (66.7)</td>
<td>62 (98.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic disease burden†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukaemia</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
<td>0.32</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>2 (1.6)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>4 (3.2)</td>
<td>4 (6.4)</td>
<td>0 (0.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>1 (0.8)</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>6 (4.8)</td>
<td>4 (6.4)</td>
<td>2 (3.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>7 (5.6)</td>
<td>5 (7.9)</td>
<td>2 (3.2)</td>
<td>0.24</td>
</tr>
<tr>
<td>TIIDM</td>
<td>89 (70.6)</td>
<td>35 (55.6)</td>
<td>54 (85.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD5D aetiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetic nephropathy</td>
<td>43 (68.3)</td>
<td>–</td>
<td>43 (68.3)</td>
<td>n/a</td>
</tr>
<tr>
<td>Chronic GN</td>
<td>6 (9.5)</td>
<td>–</td>
<td>6 (9.5)</td>
<td>n/a</td>
</tr>
<tr>
<td>Interstitial disease</td>
<td>2 (3.2)</td>
<td>–</td>
<td>2 (3.2)</td>
<td>n/a</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>1 (1.6)</td>
<td>–</td>
<td>1 (1.6)</td>
<td>n/a</td>
</tr>
<tr>
<td>Unknown (likely DN)</td>
<td>5 (7.9)</td>
<td>–</td>
<td>5 (7.9)</td>
<td>n/a</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (9.5)</td>
<td>–</td>
<td>6 (9.5)</td>
<td>n/a</td>
</tr>
<tr>
<td>Haemodialysis duration (years)</td>
<td>5 (3.6–8.3)</td>
<td>–</td>
<td>5 (3.6–8.3)</td>
<td>n/a</td>
</tr>
<tr>
<td>Type of admission†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDU</td>
<td>90 (71.4)</td>
<td>42 (66.7)</td>
<td>48 (76.2)</td>
<td>0.24</td>
</tr>
<tr>
<td>ICU</td>
<td>36 (28.6)</td>
<td>21 (33.3)</td>
<td>15 (23.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>Admission diagnostic group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>33 (26.2)</td>
<td>19 (30.1)</td>
<td>14 (22.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Respiratory</td>
<td>10 (7.9)</td>
<td>4 (6.4)</td>
<td>6 (9.5)</td>
<td>0.74</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>18 (14.3)</td>
<td>9 (14.3)</td>
<td>9 (14.3)</td>
<td>1.0</td>
</tr>
<tr>
<td>Neurological</td>
<td>6 (4.7)</td>
<td>2 (3.2)</td>
<td>0 (0.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Sepsis</td>
<td>27 (21.4)</td>
<td>13 (20.6)</td>
<td>14 (22.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Metabolic</td>
<td>30 (23.8)</td>
<td>15 (23.8)</td>
<td>15 (23.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>MSS/skin/ortho</td>
<td>2 (1.6)</td>
<td>1 (1.6)</td>
<td>1 (1.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Missed haemodialysis</td>
<td></td>
<td>15 (23.8)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>APACHEIII</td>
<td>59 (47–69)</td>
<td>54 (40–68)</td>
<td>61 (54–71)</td>
<td>0.001</td>
</tr>
<tr>
<td>APACHEIII RoD</td>
<td>0.18 (0.16)</td>
<td>0.16 (0.18)</td>
<td>0.19 (0.16)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>0.13 (0.06–0.21)</td>
<td>0.10 (0.05–0.21)</td>
<td>0.14 (0.09–0.22)</td>
<td>0.006</td>
</tr>
<tr>
<td>ICU LoS (days)</td>
<td>2.3 (0.94–3.8)</td>
<td>2.9 (1.6–5.6)</td>
<td>1.3 (0.67–2.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>ICU LoS &gt; 2 days</td>
<td>69 (54.8)</td>
<td>44 (69.8)</td>
<td>25 (39.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>ICU LoS &gt; 4 days</td>
<td>3 (23.8)</td>
<td>21 (33.3)</td>
<td>9 (14.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hospital LoS (days)</td>
<td>6.1 (3.4–30.0)</td>
<td>7.8 (3.9–13.4)</td>
<td>5.8 (2.5–11.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Mechanically ventilated</td>
<td>20 (15.9)</td>
<td>15 (23.8)</td>
<td>5 (7.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>duration (h)</td>
<td>70.3 (24.3–133)</td>
<td>70.3 (23–136)</td>
<td>72.5 (52–88)</td>
<td>0.42</td>
</tr>
<tr>
<td>Inotrope requirement</td>
<td>10 (7.9)</td>
<td>7 (11.1)</td>
<td>3 (4.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>duration (h)</td>
<td>24 (14–40)</td>
<td>25 (14–40)</td>
<td>23 (7–171)</td>
<td>0.93</td>
</tr>
<tr>
<td>Vasopressor requirement</td>
<td>45 (35.7)</td>
<td>24 (38.1)</td>
<td>21 (33.3)</td>
<td>0.58</td>
</tr>
<tr>
<td>duration (h)</td>
<td>33.2 (12–58)</td>
<td>34 (15–55)</td>
<td>31 (9–75)</td>
<td>0.56</td>
</tr>
<tr>
<td>Vasoactive therapy‡</td>
<td>48 (38.1)</td>
<td>27 (42.9)</td>
<td>21 (33.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>duration (h)</td>
<td>12 (9.5)</td>
<td>7 (11.1)</td>
<td>5 (7.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>CRRT</td>
<td>4.7 (4–84)</td>
<td>56 (4–93)</td>
<td>39 (4–75)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pre-index ED presentations (n)</td>
<td>90 (71.4)</td>
<td>28 (44.4)</td>
<td>62 (98.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>no. presentations</td>
<td>5 (2–9)</td>
<td>3 (1–6)</td>
<td>6 (5–12)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pre-index hospital admissions (n)</td>
<td>96 (78.0)</td>
<td>38 (60.3)</td>
<td>58 (92.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>no. admissions</td>
<td>4 (2–7)</td>
<td>2 (1–3)</td>
<td>6 (9–8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre index admission HDF†</td>
<td>356 (342–364)</td>
<td>363 (354–365)</td>
<td>345 (332–358)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-index ED presentations (n)</td>
<td>89 (70.6)</td>
<td>28 (44.4)</td>
<td>61 (96.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>no. presentations</td>
<td>5 (2–11)</td>
<td>3 (1–8)</td>
<td>6 (3–12)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
by ED presentations and hospital re-admissions) in the 12 months following their admission, while there is evidence that healthcare use did increase in the matched cohort with a significant decrease in HFD in the 12 months following the index ICU admission.

The lack of a mortality signal is in stark contrast to other studies. The largest of these, a registry based matched cohort study of more than 5000 Japanese CKD5D patients admitted to ICU for more than 3 days, found a higher utilisation of critical care (mechanical ventilation, vasoactive therapy), longer ICU and hospital LoS and higher ICU and 28 day mortality. From an Australian perspective, Senthuran and colleagues describe the outcome of 70 similar patients admitted to the ICU/HDU of a tertiary referral hospital between 2001 and 2006, reporting a relatively high ICU mortality of 17% and a hospital mortality of 29%. Uchino and colleagues in a 2003 study of 38 CKD5D patients in ICU receiving continuous renal replacement therapy reported an ICU mortality of 18% and a hospital mortality of 34%. However, there are at least two issues with directly comparing this study with the published literature. First, the cohorts described in the literature almost certainly reflect patients with a higher acuity of illness, and while the mortality observed in this cohort is still much lower than would be predicted from the APACHEIII score this may simply reflect the inability of

**Table 2** Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients post match (n = 126)</th>
<th>Matched cohort (n = 63)</th>
<th>CKD5D (n = 63)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-index hospital admissions (n)</td>
<td>96 (76.2)</td>
<td>36 (57.1)</td>
<td>60 (95.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>no. admissions</td>
<td>3 (2–6)</td>
<td>3 (2–4)</td>
<td>4 (2–10)</td>
<td>0.03</td>
</tr>
<tr>
<td>Post index admission HFD†</td>
<td>335 (286–355)</td>
<td>337 (282–356)</td>
<td>330 (296–352)</td>
<td>0.29</td>
</tr>
<tr>
<td>Discharge location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>97 (77.0)</td>
<td>45 (71.4)</td>
<td>52 (82.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>IHT ICU</td>
<td>4 (3.2)</td>
<td>4 (6.4)</td>
<td>0 (0.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>IHT ward</td>
<td>13 (10.3)</td>
<td>6 (9.5)</td>
<td>7 (11.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Nursing home</td>
<td>1 (0.8)</td>
<td>1 (1.6)</td>
<td>0 (0.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>ICU death</td>
<td>5 (4.0)</td>
<td>3 (4.8)</td>
<td>2 (3.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hospital death</td>
<td>11 (8.7)</td>
<td>7 (11.1)</td>
<td>4 (6.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>Deceased at census date</td>
<td>25 (19.8)</td>
<td>14 (22.2)</td>
<td>11 (17.4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Time to death</td>
<td>40.5 (9.7–299.0)</td>
<td>24.3 (5.3–72.9)</td>
<td>160.9 (15.5–464.2)</td>
<td>0.36</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>463 (204–624)</td>
<td>344 (81–652)</td>
<td>513 (406.3–624.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†Defined by Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation Outcome and Measurement Evaluation Tool (ANZICS CORE COMET) data dictionary. ‡Inotrope and/or vasopressor requirement. APACHE, Acute Physiology And Chronic Health Evaluation; CKD5D, haemodialysis-dependent chronic kidney disease; CRRT, continuous renal replacement therapy; DN, diabetic nephropathy; GN, glomerular nephritis; HFD, hospital free days; ICU, intensive care unit; IHT, interhospital transfer; LoS, length of stay; RoD, risk of death; TIIDM, type II diabetes mellitus.

**Table 3** Subgroup outcome analysis examining mortality in each group for those who had an ICU LoS of greater than 2 and 4 days

<table>
<thead>
<tr>
<th>Matched group</th>
<th>CKD5D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>Matched group LoS &gt; 2 days</td>
<td>Alive</td>
</tr>
<tr>
<td>Deceased</td>
<td>10 (22.7)</td>
</tr>
<tr>
<td>P = 0.57</td>
<td></td>
</tr>
<tr>
<td>Matched group LoS &gt; 4 days</td>
<td>Alive</td>
</tr>
<tr>
<td>Deceased</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>P = 1.0</td>
<td></td>
</tr>
</tbody>
</table>

ICU, intensive care unit; LoS, length of stay.

**Figure 3** Kaplan–Meier survival curves for the CKD5D group and matched cohort. ( ), Matched group; ( ), CKD5D.
APACHEIII to predict accurately mortality in this group. Second, there was high proportion of CKD5D patients who required critical care support having missed haemodialysis session(s), which is both highly amenable to and responds quickly to appropriate treatment (i.e. haemodialysis).

Similarly, the lack of an increase in healthcare use is at odds with national and international data which demonstrates that survivors of a critical care admission frequently have a higher healthcare requirement (hospital re-admissions and/or ED presentations) in the 12 months following an index ICU admission.17–20 This phenomenon is only partially observed in the matched cohort with a significant reduction in HFD. The lack of increase in healthcare use by this cohort may be due to several inter-related factors. These include the high proportion of patients presenting with a primary problem (missed haemodialysis) that is resolved by haemodialysis (albeit provided in an emergency setting), the high baseline healthcare use that already exists in this group, and/or the frequent reviews they receive by health professionals as a consequence of their chronic disease (three times weekly by dialysis nursing staff, and at least quarterly by a nephrologist).

There are other important differences between the published literature and the cohort reported here. First, while indigenous status is not reported in the studies by Senthuran and Uchino, it is unlikely to be as high as the 98% in this study.13,16 Second, the high rates of diabetic nephropathy observed in this cohort, and the likely associated vascular disease burden often seen with poorly controlled T1IDM, is unusual in cohorts outside of the NT, but intuitively should result in a higher mortality given the disease process often involves multiple vascular beds. Third, due to the geographical limitations of CA, CKD5D patients are tightly managed by the same team, and as a result these patients tend to be very well known by local health services. Finally, this cohort included all patients who needed ICU/HDU support including those who presented in the setting of missed dialysis session(s), for which the treatment is relatively simple and for which a low mortality would be predicted despite quite severely deranged physiology at presentation. This phenomenon of missed dialysis sessions is common in dialysis patients in the NT and occurs for several inter-related complex logistical and cultural reasons.

In order to control somewhat for the relatively high rate of admissions for ‘missing haemodialysis’ a priori subgroup analyses examining only those patients with an ICU LoS greater than 2 and 4 days were both undertaken, using ICU LoS as a surrogate marker of illness acuity. There continued to be no difference in the mortality outcomes observed, albeit that the sample size for these analyses was reduced substantially. The Kaplan–Meier plots for each group confirm that there is little medium term difference between the groups out to a median follow up of 463 days.

On the basis of these data, the APACHEIII RoD overestimated mortality. Mean RoD observed in the CKD5D cohort was 0.19, yet overall ICU mortality was substantially below this at 0.032. This is not altogether surprising given the profound disturbances in physiology (hyperkalaemia, fluid overload, azotaemia and anuria) that are observed, which are both relatively well tolerated and relatively easily ameliorated with short-term intermittent haemodialysis. This contrasts with the literature, which seems to demonstrate that APACHE is a reasonable predictor of ICU mortality in this population, and suggests that further research in this area is warranted.11,16

**Limitations and strengths**

This study has several strengths. It is the first study examining the medium term outcomes of a unique group of Indigenous Australian CKD5D patients who require admission with a life threatening illness. There was a high follow-up rate, and this cohort is large by Australian standards. While matching the cohort was difficult (due primarily to the absence of a non-CKD5D equivalent to ‘missing haemodialysis’), the matching process produced a cohort that had a similar APACHEIII RoD. There were no CKD5D patients lost to follow up, while the high proportion of NTG clinics (approximately 67% in the catchment area), in conjunction with the close working relationship between non-Government clinics and the hospital, mean that mortality is recorded with a high degree of confidence.

Several limitations make the generalisability of this study difficult. First, the CKD5D population in CA is unique – relatively young, with high rates of diabetic nephropathy and a relatively long median duration of haemodialysis (5 years). Furthermore, there was a high proportion of patients admitted with a diagnosis of ‘missing haemodialysis’ which would be expected to have a very low mortality rate once treatment has been implemented. Third, as a database study it is reliant on the accurate coding of patients and the accurate entry of data. The relatively high rate (7.4%) of patients which were initially coded as CKD5D who did not meet the ANZICS COMET definition raises the possibility that inaccurate coding has occurred. Fourth, there were difficulties encountered in the matching process – there is no non-CKD5D diagnostic category that is equivalent to missed haemodialysis, and despite matching for APACHEIII score there remains a statistically significant difference in
the scores between the groups (although given that there was no statistically significant difference in the APACHEIII RoD it could be argued that the difference in score is not clinically important). Similarly, it is questionable whether APACHEIII scoring is appropriate at all for the subgroup of CKD5D patients presenting in the setting of having missed dialysis session(s). These patients frequently have profoundly deranged physiological parameters that are highly amenable to treatment (namely haemodialysis), and which respond very rapidly. This is seen in the proportion of patients who have an ICU LoS less than 2 days in each of the groups. Finally, there is a significant difference in the proportion of indigenous patients in each arm.

Conclusion

The high morbidity and mortality burden that is suggested by the critical care literature for patients with CKD5D requiring critical care support is not seen in this cohort in CA. Furthermore, unlike non-CKD5D patients, there is no indication in this cohort that an index ICU admission results in an increase in healthcare use and thus does not confer a morbidity burden. Additional research is required to ascertain the reasons for this. The presence of dialysis-dependent renal failure by itself should not affect the decision to offer critical care support.

Acknowledgements

Alice Springs Hospital Renal-ICU Research Group: ICU: Dr Penny Stewart; Dr Greg McAnulty; and Dr Sajiv Cherian; Dr David Fernandes; Dr Sajjan Thomas; Dr Sajith Nayar; and Dr Pratish George.

References

11 Juneja D, Prabhu MV, Gopal PB, Mohan S, Sridhar G, Nayak KS. Outcome of patients with end stage renal disease admitted to an intensive care unit in India. Renal Fail 2010; 32: 69–73.
Prevalence of advance care directives in the community: a telephone survey of three Australian States

Ben P. White,1 Lindy Willmott,1 Cheryl Tilse,2 Jill Wilson,2 Michele Ferguson,3 Joanne Aitken,4 Jeffrey Dunn,5 Deborah Lawson,6 Angela Pearce7 and Rachel Feeney

1Australian Centre for Health Law Research, Queensland University of Technology, 2School of Nursing, Midwifery and Social Work, The University of Queensland, 3The University of Queensland, Queensland University of Technology, and 4Cancer Council Queensland, Brisbane, and 5University of Southern Queensland, Toowoomba, Queensland, 6Cancer Council Victoria, Melbourne, Victoria, and 7Cancer Council New South Wales, Sydney, New South Wales, Australia

Abstract

Background: The community prevalence of advance care directives (ACD) is low despite known benefits of advance care planning for patients, families and health professionals.

Aim: To determine the community prevalence of instructional and appointing ACD in New South Wales, Victoria and Queensland and factors associated with completion of these documents.

Methods: A telephone survey of adults living in New South Wales, Victoria and Queensland (n = 1175) about completion of instructional ACD (making their own decisions about future healthcare) and appointing ACD (appointing another to decide). Quota sampling occurred based on population size by state, gender and age, with oversampling in smaller jurisdictions (Victoria and Queensland).

Results: Overall response rate was 33%. Six per cent of respondents reported completing an instructional ACD while 12% reported completing an appointing ACD. Female gender, higher educational level, personal experience of a major health scare and being widowed were significant predictors of completing an instructional ACD. Older age, higher educational level and being widowed were significant predictors of completing an appointing ACD.

Conclusions: Despite long-standing efforts to increase advance care planning, community prevalence of ACD remains low, particularly for instructional ACD. This study found some different predictors for instructional ACD compared with appointing ACD, and also a potential role for experiential factors in triggering uptake. These findings suggest supplementing general community awareness campaigns with more nuanced and targeted efforts to improve ACD completion.

Introduction

Enhancing advance care planning (ACP) is an Australian and international policy priority. There have been repeated calls to increase ACP from governments, medical associations and patient and consumer groups.1-4 In addition to providing patient-centred care that respects choice, ACP can benefit families and healthcare professionals.5
ACP can range from an informal conversation through to the completion of legal documents, known as advance care directives (ACD). Noting terminology is vexed in this area, we adopt the Australian Health Ministers’ Advisory Council’s recognition of two types of ACD. The first is an instructional advance directive or ‘living will’ (hereafter ‘instructional ACD’). This allows a person to make decisions or state goals of care for future medical treatment. All Australian states and territories (except New South Wales and Tasmania) have legislation creating instructional ACD. Instructional ACD in New South Wales and Tasmania are recognised by the common law (law made by judges rather than Parliament).5

The second type of ACD appoints a person to make decisions for another in case of future lost capacity (hereafter ‘appointing ACD’). Often called an enduring guardian or power of attorney, all Australian jurisdictions have legislation that facilitate these appointments.7

Despite its significance for health policy, there is only limited research on the prevalence of ACD. The first national study of community prevalence found that 14% of Australians had an instructional ACD.8 A South Australian study found a community prevalence of 12% for instructional ACD in that State and 13 and 11% respectively for two types of appointing ACD (enduring powers of guardianship and medical powers of attorney).9 Other research has focused on ACD completion in particular settings, such as residential aged care and hospital.10–14 There is also limited and inconclusive research on who completes ACD. For example, White et al. found that demographic variables had limited ability to predict completion of an instructional ACD.8

This lack of data about who makes ACP, how often and why impedes the identified policy goal to increase ACP. A dearth of reliable evidence to improve end-of-life care was a key finding of the Productivity Commission’s recent review of this field.3 The Commission called for a national end-of-life data strategy, including data on the prevalence of ACP. This research responds to that call and provides a much-needed evidence base to address the long-standing policy challenge of increasing community uptake of ACP.

Methods
A telephone survey was conducted from 4 March to 26 April 2016 about Australian adults’ experience with end-of-life decision-making and perceptions of law in this area. The survey was pre-tested (n = 12, convenience sample) and then piloted (n = 20) by trained and experienced interviewers from the Computer Assisted Telephone Interview laboratory at The University of Queensland. During data collection, one in eight interviews was monitored by a supervisor.

The sample comprised adult residents of New South Wales, Victoria and Queensland. These states were chosen because of similarities and differences in ACD documentation and law, and because they are Australia’s most populous states (78% of national population15). To ensure an approximately age-representative sample within each state, targets were applied to age groups (18–24, 25–39, 40–59, ≥60 years) for each gender based on Australian Bureau of Statistics population estimates.15 Queensland and Victoria (the two smallest jurisdictions) were oversampled to yield sufficient data for robust statistical analyses. Sampleworx, a commercial sample provider, supplied randomly generated and verified landline (40%) and mobile telephone numbers (60%) (validated every 6 months). A total of 10 610 telephone numbers were contacted to obtain the state quotas, resulting in 3571 eligible calls. Ineligible calls included unanswered calls and calls to an answering machine, a fax number, or to a person located in a state outside the study or under 18.16

Ethical approval was obtained from the Queensland University of Technology University Human Research Ethics Committee (1500001069) and The University of Queensland Behavioural and Social Sciences Ethical Review Committee (2016000068). All participants gave their informed consent prior to their inclusion in the study.

Measures
The survey instrument contained 32 questions covering: perceived and actual knowledge of the law about ACP and end-of-life decision-making; sources of that knowledge; experiences of end-of-life decision-making (including engagement with ACP); demographics (Table 1); and self-rated health status over the past 12 months.

This paper reports findings from survey questions about completion of ACD (Box 1). First, participants were given an explanation of the difference between instructional and appointing ACD. Participants were then asked if they had completed each of these documents. Interviewers provided the name of the instructional or appointing ACD in the participant’s jurisdiction if queried.

Statistical analysis
Data were analysed using Stata version 14 (StataCorp LLC). Sample data were weighted for gender, age, state and education level to represent Australian Bureau of Statistics population distributions.15 Descriptive analyses examined the prevalence of ACD completion. Bivariate analyses (cross tabulations and Chi-squared tests)
explored variations in individual ACD completion across demographic variables and types of end-of-life decision-making experience. For descriptive and bivariate analyses, both weighted and unweighted analyses were undertaken and results compared; weighted estimates for these analyses are reported here.

A multinomial logistic regression model was used to explore the relative strength of the same demographic and personal end-of-life experience variables on completion of either an instructional or appointing ACD, and on completion of both documents. The categorical response variable had four categories: no ACD; instructional ACD only; appointing ACD only and both instructional and appointing ACD.

The multivariable analyses (odds ratios) reported here are not weighted as they include the weighted demographics as independent variables. For all analyses, statistical significance was set at 5% ($P \leq 0.05$).

Results

The response rate was 33% with 1175 surveys completed from 3571 eligible telephone calls. The combined dual-frame sample was representative for gender and remoteness, but was older and more educated than the combined populations of the three states. People identifying as Aboriginal and Torres Strait Islanders and those born in Australia were underrepresented (Supporting Information Table S1).

Prevalence of ACD

Six per cent of respondents reported completing an instructional ACD. Twice as many respondents (12%) reported completing an appointing ACD. Less than 4% of respondents reported completing both types of ACD while 15% reported completing at least one of them (Table 2).

Who has ACD

The strongest predictor of completing an appointing ACD is age with those over 55 almost 6 times more likely to have one compared to those under 35 years (Table 1). Educational level and marital status were also significant predictors. People with a bachelor degree or postgraduate qualifications were more than twice as likely to have an appointing ACD compared to those with school education only. People whose spouses had died were approximately twice as likely to have an appointing ACD as married participants.

Age was not a significant predictor of completing an instructional ACD. However, women were three times more likely to have one than men (Table 1). People who had had their own ‘major health scare’ were almost three times more likely to have an instructional ACD. Education was again relevant with people having a postgraduate qualification more likely than others to have this document. Finally, although only approaching significance ($P = 0.05$), being widowed increased the odds of having an instructional ACD by three times.

When considering who has both an instructional ACD and appointing ACD, none of the above factors was significant. However, those living in Queensland were twice as likely as those in other states to have completed both documents (Table 1), as were people who had looked after a partner, adult family member or friend with a chronic or terminal illness.
Discussion

Community prevalence of both ACD is low and particularly for instructional ACD (6.2% for instructional ACD and 11.9% for appointing ACD). This is striking when compared with community prevalence rates of financial enduring powers of attorney (30%) and wills (59%).

Reasons advanced for this include avoiding consideration of mortality and ill-health poor public awareness of existence and utility of ACD and the complexity of existing legal frameworks, including variation across Australian jurisdictions.

While policy-makers and others urge people to undertake ACP, the low uptake of ACD shows challenges in Australia remain. This is a policy problem globally.

Although international comparisons should be undertaken cautiously given differences in populations and health systems as well as legal frameworks and terminology, community prevalence is estimated to range from 18% to 37% in the United States and 3% to 19% in Europe.

These findings about prevalence differ from those of the earlier national community prevalence study. That 2014 study did not include appointing ACD and focused only on instructional ACD, finding a prevalence of 14.4% nationally (NSW 13.3%; Queensland 19%; Victoria 13.4%). That earlier result is strikingly similar to the finding in this study of 14.6% prevalence of having at least one of an instructional or appointing ACD (NSW 12.7%; Queensland 16.8%; Victoria 14.6%).

Table 1 Characteristics of participants who had an ACD†

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Instructional ACD only</th>
<th>Appointing ACD only</th>
<th>Both instructional and appointing ACD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR CI P-value</td>
<td>OR CI P-value</td>
<td>OR CI P-value</td>
</tr>
<tr>
<td>End-of-life decision-making experience</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Looking after a partner, adult family member or friend with a chronic or terminal illness</td>
<td>1.37 (0.62–3.04) (0.432)</td>
<td>1.24 (0.76–2.02) (0.392)</td>
<td>2.24* (1.08–4.66) (0.030)</td>
</tr>
<tr>
<td>A partner, adult family member or friend receiving medical care as they approached the end of their lives</td>
<td>1.02 (0.45–2.32) (0.954)</td>
<td>1.41 (0.84–2.38) (0.198)</td>
<td>1.21 (0.56–2.65) (0.626)</td>
</tr>
<tr>
<td>Your own major health scare</td>
<td>2.82** (1.37–5.79) (0.005)</td>
<td>1.09 (0.67–1.77) (0.721)</td>
<td>1.36 (0.70–2.64) (0.358)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–34</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>35–54</td>
<td>0.72 (0.27–1.95) (0.519)</td>
<td>2.22 (0.95–5.18) (0.066)</td>
<td>1.44 (0.43–4.81) (0.555)</td>
</tr>
<tr>
<td>55+</td>
<td>1.32 (0.49–3.53) (0.578)</td>
<td>5.91*** (2.58–13.55) (0.000)</td>
<td>2.92 (0.90–9.53) (0.076)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>3.08** (1.42–6.67) (0.004)</td>
<td>0.96 (0.63–1.46) (0.841)</td>
<td>1.20 (0.65–2.22) (0.563)</td>
</tr>
<tr>
<td>State</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSW</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>QLD</td>
<td>1.60 (0.72–3.55) (0.249)</td>
<td>1.18 (0.72–1.94) (0.520)</td>
<td>2.19* (1.05–4.57) (0.036)</td>
</tr>
<tr>
<td>VIC</td>
<td>1.05 (0.45–2.44) (0.910)</td>
<td>0.89 (0.53–1.47) (0.643)</td>
<td>1.13 (0.50–2.52) (0.772)</td>
</tr>
<tr>
<td>Relationship status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Single, never married</td>
<td>0.66 (0.22–1.96) (0.454)</td>
<td>0.75 (0.37–1.54) (0.438)</td>
<td>0.53 (0.17–1.65) (0.376)</td>
</tr>
<tr>
<td>Separated but not divorced</td>
<td>0.00 (0.00–1) (0.982)</td>
<td>0.27 (0.04–2.05) (0.206)</td>
<td>0.51 (0.07–3.93) (0.516)</td>
</tr>
<tr>
<td>De facto relationship (including same-sex)</td>
<td>1.48 (0.55–4.02) (0.441)</td>
<td>0.64 (0.26–1.55) (0.321)</td>
<td>0.22 (0.03–1.66) (0.414)</td>
</tr>
<tr>
<td>Divorced</td>
<td>0.55 (0.12–2.55) (0.443)</td>
<td>0.65 (0.28–1.53) (0.327)</td>
<td>1.51 (0.62–3.65) (0.360)</td>
</tr>
<tr>
<td>Widowed</td>
<td>3.00 (1.00–8.99) (0.050)</td>
<td>2.35* (1.14–4.84) (0.021)</td>
<td>1.13 (0.35–3.64) (0.843)</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School only</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>TAFE/Technical Certificate/Diploma</td>
<td>0.47 (0.13–1.71) (0.253)</td>
<td>1.65 (0.95–2.89) (0.076)</td>
<td>1.11 (0.51–2.40) (0.794)</td>
</tr>
<tr>
<td>Bachelor degree</td>
<td>2.19 (0.94–5.13) (0.070)</td>
<td>1.96 (1.11–3.44) (0.020)</td>
<td>1.11 (0.48–2.56) (0.801)</td>
</tr>
<tr>
<td>Postgraduate qualification</td>
<td>3.71** (1.50–9.22) (0.005)</td>
<td>2.25* (1.18–4.30) (0.014)</td>
<td>1.56 (0.63–3.85) (0.337)</td>
</tr>
</tbody>
</table>

*P < 0.05. **P < 0.01. ***P < 0.001. Base category = No ACD; (missing data for 2 participants). ACD, advance care directive; CI, confidence interval; OR, odds ratio; TAFE, Technical and Further Education.
Comparing these studies may shed important light on methodological issues in research about ACP and ACD. Despite the 2014 study explaining the concept of instructional ACD, the absence of a corresponding explanation about an appointing ACD means participants may not have differentiated between these documents. This could suggest that participants responded positively to the question about an ACD for either type of ACD, despite the 2014 study only asking about instructional ACD. This interpretation may help explain similarities in prevalence rates for both studies. Confusion about terminology for ACP and ACD was noted above and this exists in the community. Examining these two studies together suggests the importance of explaining to participants the suite of ACP and ACD documents and how they differ. Limitations noted in both studies include that results depend upon participants’ understanding of the questions and accurate responses.

The significantly increased likelihood of widowed people having an instructional or appointing ACD could be prompted by experiencing a spouse’s death. This is both a demographic characteristic and a very relevant experiential factor (discussed below) in that it involves direct contact with end-of-life issues. It may also be a reflection that the person who would ordinarily decide for them (their spouse) is now gone. However, this study cannot make claims about causation because it did not collect data about the reasons for completing ACD nor whether being widowed preceded making an ACD. Nevertheless, the greater completion of ACD by widowed people is a new finding in the Australian setting and is consistent with studies conducted in a Canadian province and in Belgium (albeit in relation to euthanasia ACD). Although some characteristics associated with completion of both types of ACD were similar (being widowed and higher educational level), there were important differences. For appointing ACD, age was strongest predictor which reflects the tendency found internationally for more planning for, and experience of, death and illness at a later age. For instructional ACD, being female was associated with higher completion of this document, again consistent with some international studies, although others found no gender-based differences.

Most significant, however, is the finding that instructional ACD were associated with a person who has had their own ‘health scare’. While causation cannot be determined for reasons noted above, this finding is important because there is little evidence about the role of health and experiential factors in predicting ACD completion. A Canadian single-province study also found an association between ACD completion and experiences, such as having a close relation or friend die, caring for them as they were dying, and being involved in end-of-life decision-making. Further, small Australian qualitative studies have found that declining health or an illness diagnosis can initiate ACP processes as can concerns about suffering at the end of life. More research is needed to understand whether and if so, how, a person’s experiences may trigger completing ACD, particularly given the limited predictive power of demographic characteristics.

These findings about different associations for instructional and appointing ACD should prompt more nuanced approaches to increasing uptake. There are differences in who are completing these two documents, and different reasons why they are completed. This is not surprising given the different purposes of the two documents and their utility at various life stages. For example, a person with a known illness trajectory may be more motivated to complete an instructional ACD making concrete decisions about their future healthcare than a person who is currently well. These differences suggest generic efforts to improve ACP generally may not be effective. This is highlighted by the fact that only 3.6% of people have both ACD. As noted, there may be health events that trigger instructional ACD, but age-related prompts, such as wider planning exercises, that initiate appointing ACD. These occasions need to be utilised effectively, but sensitively, to create awareness of ACD when these opportunities present. Conversely, understanding who is less likely to have a type of ACD may inform development of more specific engagement strategies. The lower completion by men of instructional ACD is an example.

One limitation of this research is its response rate of 33%. However, this is comparable with other large community telephone surveys examining end-of-life issues and may reflect community reluctance or disinterest in discussing these topics. Accordingly, non-response bias cannot be ruled out. Second, the sample was overeducated compared to the sample

<table>
<thead>
<tr>
<th>Completion of ACD</th>
<th>NSW</th>
<th>QLD</th>
<th>VIC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instructional ACD only</td>
<td>5.0</td>
<td>8.5</td>
<td>6.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Appointing ACD only</td>
<td>10.3</td>
<td>13.4</td>
<td>12.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Both instructional ACD and appointing ACD</td>
<td>2.7</td>
<td>5.1</td>
<td>3.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Either instructional ACD or appointing ACD</td>
<td>12.7</td>
<td>16.8</td>
<td>15.2</td>
<td>14.6</td>
</tr>
</tbody>
</table>

1Numbers and percentages may not add to totals or 100% as data are weighted and rounded to whole decimal. ACD, advance care directive.
population. However, there was an approximately representative sample within each state, and data were weighted to reflect underlying population distributions. Third, data were collected at a single time point so it was not possible to determine whether an ACD was completed before or after (in response to) demographic or experiential events. This study also has strengths, especially in relation to earlier national prevalence work, including explicitly explaining both types of ACD. However, as noted above, these results rely on participants’ understanding of the questions. Another strength is that this study went beyond demographic characteristics to include experiential factors, such as previous end-of-life experiences and health status, which previous Australian population level studies have not done.

Conclusion

Community prevalence of ACD in Australia remains low, particularly when compared with other planning documents, such as financial enduring powers of attorney and wills. This is despite extensive efforts to increase rates of ACP by state and federal governments, health services and non-government organisations. This suggests new approaches are needed to engage the community, or specific cohorts in the community, in planning for their future health. To supplement general public awareness campaigns, which some suggest have had only modest success, this research suggests a more nuanced approach in three ways.

First, instructional and appointing ACD have different purposes and are completed for different reasons. Community engagement that distinguishes clearly the types of ACD and potential role in ACP may be more effective than generic encouragement to plan for the future. Second, findings about groups who are more and less likely to complete one or both types of ACD can be used to engage particular cohorts more effectively. For example, knowledge that women are three times more likely than men to complete an instructional ACD may point to more gender-specific ACP resources. Third, although caution is needed in inferring causation, this research identified key end-of-life/health experiences (e.g. being widowed and having a major health scare) as being associated with ACD completion. Although further research is needed, this suggests considering whether key experiential factors may create an environment in which people are receptive to ACD completion. Of course, the nature of these experiences points to engaging with these cohorts very sensitively. These three proposals align with the Productivity Commission’s recommendation for a data-driven approach to designing end-of-life care policy and advance the established policy imperative to increase uptake of ACP.

Acknowledgements

We acknowledge the contribution of the Computer Assisted Telephone Interview (CATI) laboratory, Institute for Social Science Research (ISSR) at The University of Queensland (UQ), particularly Sue York (research services manager), Joseph Byrne (research analyst and programmer), Elizabeth Kennedy (research officer) and Michele Haynes (programme leader, Research Methods and Social Statistics, ISSR). The invaluable statistical support from Michele Haynes and Francisco Perales (Research Fellow, ISSR) is also gratefully acknowledged.

References

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OpenDocument


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

Table S1. Descriptive statistics of sample.
Safety and outcomes of $^{177}$Lu-DOTATATE for neuroendocrine tumours: experience in New South Wales, Australia

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Key words
neuroendocrine tumour, peptide receptor radionuclide therapy (PRRT), $^{177}$Lu-DOTATATE, radiopharmaceutical, clinical protocol.

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Abstract
Background: Peptide receptor radionuclide therapy with $^{177}$Lu-DOTATATE is a promising treatment for inoperable or metastatic neuroendocrine tumours (NET). In 2015, the NSW Ministry of Health provided funding for $^{177}$Lu-DOTATATE treatment of NET under an evaluation framework.

Aims: To examine the safety and outcomes of NET patients treated with $^{177}$Lu-DOTATATE under the evaluation framework and assess the statewide implementation of the NSW Lutate therapy referral and protocol for neuroendocrine cancer patients.

Methods: A quality of care clinical audit was conducted on all NET patients treated with $^{177}$Lu-DOTATATE from October 2010 to October 2015 at St George Hospital, and from August 2013 to March 2017 at Royal North Shore Hospital. Percentage of patients who met protocol selection criteria was calculated. Survival was estimated using the Kaplan–Meier method. Adjusted regression analyses assessed associations between key clinical factors and outcomes.

Results: A total of 279 patients was treated. Statewide protocol implementation led to an increase from 60.5 to 83.8% in patients meeting selection criteria. Estimated median overall survival was significantly longer for patients who met selection criteria compared with those who did not (50.7 vs 34.2 months) ($P = 0.018$). This was driven by the significantly worse overall survival in patients who failed exclusion criteria ($P < 0.001$). $^{177}$Lu-DOTATATE was well tolerated with haematological, renal and hepatic treatment-related serious adverse events experienced by 9.7, 0.4 and 0.4% of patients respectively.

Conclusions: $^{177}$Lu-DOTATATE is a promising treatment for advanced NET. Superior survival in patients who met selection criteria emphasise the importance of protocol adherence.

Introduction

Neuroendocrine tumours (NET) are a heterogenous group of tumours that originate from neuroendocrine cells in a variety of locations.1 The incidence of NET is increasing.2–5 In New South Wales (NSW), the age standardised incidence rate increased from 8.7 per 100 000 in 1982 to 11.0 per 100 000 in 2000 and 14.1 per 100 000 in 2013.6 The rising incidence is likely due to increased detection and improvements in the classification of NET.4,7

Most NET are asymptomatic until the tumour has metastasised. Patients are often diagnosed late and at an advanced stage.7 A range of treatment options is available for patients with advanced NET, including somatostatin analogues (SSA), chemotherapy, targeted therapies and peptide receptor radionuclide therapy (PRRT).8 PRRT is a promising treatment for inoperable or metastatic NET and uses radiolabeled SSA to target radiation to tumours that express somatostatin receptors.
NET typically express a high number of somatostatin receptors on their cell membranes. Results from the phase III NETTER-1 trial, published in January 2017, showed that PRRT treatment with $^{177}$Lu-DOTATATE significantly improved progression-free survival (PFS) and suggested an overall survival (OS) benefit, when compared with treatment with octreotide long-acting repeatable in patients with well-differentiated, metastatic midgut NET. Results from case series have mostly focused on gastroenteropancreatic NET (GEP NET) and have also been encouraging.\textsuperscript{10–18}

$^{177}$Lu-DOTATATE is an unregistered medicine in Australia accessed via the Therapeutic Goods Administration’s Special Access Scheme. Historically, $^{177}$Lu-DOTATATE treatment in NSW had been self-funded by patients. It was recognised that some patients could benefit substantially from the use of $^{177}$Lu-DOTATATE as a second or subsequent line of therapy for NET. In 2015, the NSW Ministry of Health provided statewide funding for $^{177}$Lu-DOTATATE to be provided at two hospitals under an evaluation framework. At this time, high-quality safety and efficacy data were still pending and the NETTER-1 results had not been published. Under the evaluation framework, the \textit{NSW Lutate therapy referral and protocol for neuroendocrine cancer patients (Lutate protocol)}\textsuperscript{19} was implemented to optimise patient selection and standardise therapy. The Lutate protocol was formulated with expert clinical input based on the available evidence and based largely on the joint International Atomic Energy Agency, European Association of Nuclear Medicine, and Society of Nuclear Medicine and Molecular Imaging guidelines.\textsuperscript{20} The evaluation was also to contribute to the evidence base regarding safety and effectiveness.

As part of the evaluation, a retrospective clinical audit was conducted of the complete case series of NET patients treated with $^{177}$Lu-DOTATATE at both hospitals. The audit aimed to assess the safety and outcomes of patients treated with $^{177}$Lu-DOTATATE and to evaluate the statewide implementation of the Lutate protocol.\textsuperscript{19}

**Methods**

A quality of care clinical audit was conducted on NET patients treated with $^{177}$Lu-DOTATATE at Nuclear Medicine departments at two hospitals in NSW, Australia. This was a case note review of medical records available to the Nuclear Medicine departments. Data in the medical records were recorded primarily for clinical care and not specifically for the purpose of the evaluation. The St George Hospital audit was completed in April 2016, and reviewed all patients who received their first cycle of $^{177}$Lu-DOTATATE between October 2010 and October 2015. After reviewing the audit results from St George Hospital, the Lutate Evaluation Governance Group recommended auditing Royal North Shore Hospital as their patient numbers were gradually increasing and had reached a sufficient level to justify an audit. The Royal North Shore Hospital audit was completed in March 2017, and all patients who started $^{177}$Lu-DOTATATE therapy between August 2013 and March 2017 were reviewed. For quality assurance purposes, the audit included a double review of a random 10% of patient files by three independent auditors. Data from medical records were supplemented with vital status information extracted from the NSW Cancer Registry in March 2018.

**Patients**

All audited patients were included in this analysis. The Lutate protocol\textsuperscript{19} was implemented from January 2015. Patient suitability (inclusion) and exclusion criteria are listed in Table 1. Although most patients (73.5\%) were referred for treatment before formal protocol implementation, patient selection criteria and treatment protocols at both hospitals before 2015 were broadly consistent with the Lutate protocol.\textsuperscript{19}

**Treatment**

$^{177}$Lu and peptide were obtained from commercial radiopharmaceutical suppliers, including IDB Holland (Baarle-Nassau, The Netherlands), ITG Isotope Technologies (Garching, Germany) and Australian Nuclear Science and Technology Organisation (Lucas Heights, Australia). $^{177}$Lu-DOTATATE was prepared locally in the Nuclear Medicine department in accordance with supplier recommendations. $^{177}$Lu-DOTATATE treatment was intended to be administered over four cycles, 8 weeks (range 6–12 weeks) apart, with 7.5–8 GBq of $^{177}$Lu-DOTATATE infused intravenously at each cycle. To reduce the likelihood and severity of nausea and vomiting, premedications were administered based on local preference, but typically comprised dexamethasone and a selective 5-HT3 receptor antagonist. A renoprotective amino acid infusion containing 25 g lysine and 25 g arginine per litre or commercial Baxter Synthamin containing 5.8 g lysine and 11.5 g arginine per litre was administered over 3–4 h starting from 30 min before $^{177}$Lu-DOTATATE administration. Radiosensitising chemotherapy was to be administered before, and after, each cycle of $^{177}$Lu-DOTATATE, unless contraindicated in individual clinical situations. This generally comprised of capecitabine 750 mg administered twice daily for 1 week prior to and 2 weeks following $^{177}$Lu-DOTATATE therapy.
Outcomes

Routine haematological, kidney and liver function tests were performed 4 weeks after each 177Lu-DOTATATE cycle and 2 weeks before the next 177Lu-DOTATATE administration. Adverse events (AE) were gleaned from medical records and reported using Common Terminology Criteria for Adverse Events v4.03. Treatment-related serious adverse events (SAE) were defined as Common Terminology Criteria for Adverse Events v4.03 grade 3 or 4 AE that had a reasonable possibility, as reviewed by the clinical teams, of being caused by 177Lu-DOTATATE and/or concomitant medications administered as part of the protocol. A repeat 68Ga-DOTATATE scan was performed following the fourth cycle of 177Lu-DOTATATE treatment. Additional 68Ga-DOTATATE and restaging computed tomography scans were performed as clinically required. Disease progression was defined as clinical progression or new and/or enlarged lesions on radiological scans as confirmed by the clinical team. OS, disease-specific survival (DSS) and PFS were calculated from the day of the first 177Lu-DOTATATE cycle to the date of death, date of death from the NET or date of documented disease progression respectively. Deaths with an unknown cause were censored in DSS analyses.

Table 1  Adherence to patient selection criteria for 177Lu-DOTATATE treatment (n = 279)

<table>
<thead>
<tr>
<th>Suitability criteria</th>
<th>Yes</th>
<th>No</th>
<th>Not recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Histologically proven NET of any origin</td>
<td>261 (93.5)</td>
<td>11 (3.9)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>2. Locally advanced and/or inoperable (metastatic) disease</td>
<td>279 (100.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. Failed first line systemic therapy</td>
<td>249 (89.2)</td>
<td>30 (10.8)</td>
<td>0</td>
</tr>
<tr>
<td>4. Progressive disease demonstrated radiologically while on somatostatin analogue therapy or uncontrolled symptoms despite systemic therapy</td>
<td>222 (79.6)</td>
<td>55 (19.7)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>5. Presence of somatostatin-receptors on the known tumour lesions demonstrated by 68Ga-DOTATATE scan within past 6 months. The uptake of the NET lesions should be at least as high as normal liver uptake.</td>
<td>257 (92.1)</td>
<td>22 (7.9)</td>
<td>0</td>
</tr>
<tr>
<td>6. ECOG status 0–2</td>
<td>78 (28.0)</td>
<td>0</td>
<td>201 (72.0)</td>
</tr>
<tr>
<td>7. Patient’s written voluntary informed consent</td>
<td>268 (96.1)</td>
<td>21 (0.7)</td>
<td>91 (3.2)</td>
</tr>
<tr>
<td>All suitability criteria</td>
<td>199 (71.3)</td>
<td>80 (28.7)</td>
<td>0</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Significant co-morbidity that is likely to interfere with the therapy</td>
<td>0</td>
<td>279 (100.0)</td>
<td>0</td>
</tr>
<tr>
<td>2. ECOG 3 or 4</td>
<td>0</td>
<td>78 (28.0)</td>
<td>201 (72.0)</td>
</tr>
<tr>
<td>3. Uncontrolled congestive heart failure or carcinoid heart disease</td>
<td>0</td>
<td>279 (100.0)</td>
<td>0</td>
</tr>
<tr>
<td>4. Patients unable to interrupt somatostatin analogue therapy</td>
<td>0</td>
<td>61 (21.9)</td>
<td>218 (78.1)</td>
</tr>
<tr>
<td>5. Life expectancy less than 12 weeks</td>
<td>0</td>
<td>21 (7.5)</td>
<td>258 (92.5)</td>
</tr>
<tr>
<td>6. Pregnancy</td>
<td>0</td>
<td>267 (95.7)</td>
<td>12 (4.3)</td>
</tr>
<tr>
<td>7. Renal impairment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• GFR &lt; 40 mL/min/1.73 m²</td>
<td>1 (0.4)</td>
<td>277 (99.3)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>8. Impaired bone marrow reserve:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Haemoglobin ≤9.0 g/dL</td>
<td>8 (2.9)</td>
<td>271 (97.1)</td>
<td>0</td>
</tr>
<tr>
<td>• WBC ≤2 x 10^9/L</td>
<td>0</td>
<td>279 (100.0)</td>
<td>0</td>
</tr>
<tr>
<td>• Absolute neutrophil count &lt;1.0 x 10^9/L</td>
<td>0</td>
<td>276 (98.9)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>• Platelet count ≤75 x 10^9/L</td>
<td>1 (0.4)</td>
<td>278 (99.6)</td>
<td>0</td>
</tr>
<tr>
<td>9. Hepatic impairment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Total serum bilirubin ≥75 μmol/L or ≥1.5 x upper limit normal (unless Gilbert’s syndrome)</td>
<td>1 (0.4)</td>
<td>274 (98.2)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>• Serum albumin ≥25 g/L</td>
<td>7 (2.5)</td>
<td>268 (96.1)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>10. Discordant FDG uptake with significant disease that is FDG avid but 68Ga-DOTATATE non-avid</td>
<td>5 (1.8)</td>
<td>106 (38.0)</td>
<td>168 (60.2)</td>
</tr>
<tr>
<td>Any exclusion criteria</td>
<td>22 (7.9)</td>
<td>257 (92.1)</td>
<td>–</td>
</tr>
<tr>
<td>Met all selection criteria</td>
<td>186 (66.7)</td>
<td>93 (33.3)</td>
<td>–</td>
</tr>
</tbody>
</table>

†Written informed consent form dated after the start of 177Lu-DOTATATE therapy. ‡Written informed consent form could not be located. ECOG, Eastern Cooperative Oncology Group; FDG, fluorodeoxyglucose; GFR, glomerular filtration rate; NET, neuroendocrine tumour; WBC, white blood cell.
Statistical analysis

Percentage of patients who met (passed) protocol selection criteria was calculated overall and for time periods before and after implementation of the Lutate protocol.\textsuperscript{19} Kaplan–Meier analysis estimated median survival with associated 95% confidence intervals (95% CI). Log-rank tests compared OS between sub-groups stratified by primary tumour site and adherence to selection criteria. Midgut NET were defined as NET of the small bowel, appendix and right ascending colon.

Adjusted regression analyses assessed associations between primary tumour site, Ki-67 proliferation index and adherence to selection criteria with OS, treatment-related SAE or treatment completion (completion of four or more cycles during the initial course of \textsuperscript{177}Lu-DOTATATE therapy). Patients who had future cycles planned and had not finished their initial \textsuperscript{177}Lu-DOTATATE course were excluded from analyses of treatment completion. Likelihood of treatment completion was estimated with a Bayesian logistic regression model with risk expressed as odds ratios. Risk of a treatment-related SAE was estimated with a Bayesian Poisson regression model including an offset for the number of cycles of treatment received with risk expressed as incidence rate ratios. OS was estimated with a proportional hazards regression model with risk expressed as hazard ratios (HRs). All models included risk adjustment for age, sex and comorbidity. \(P\)-values less than 0.05 were considered statistically significant. Analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing).

Results

Patients

A total of 279 NET patients received \textsuperscript{177}Lu-DOTATATE treatment. Patient and clinical characteristics are presented in Table 2. Median age at the time of \textsuperscript{177}Lu-DOTATATE treatment was 63 years (range 15–89 years; interquartile range 53–70 years). Small bowel was the most common primary tumour site (37.1%) and most tumours (64.2%) had a Ki-67 proliferation index of 20% or less. Only five patients did not receive any prior therapy.

All 279 patients were assessed against patient suitability and exclusion criteria (Table 1) in the Lutate protocol.\textsuperscript{19} Overall, 186 (66.7%) patients met all selection (suitability and exclusion) criteria and were eligible for \textsuperscript{177}Lu-DOTATATE treatment (Table 2). The most common reason for failing suitability criteria was an absence of progressive disease while on SSA therapy or uncontrolled symptoms despite systemic therapy (19.7%). For patients not treated for either progressive disease or uncontrolled symptoms, reasons for \textsuperscript{177}Lu-DOTATATE included extent of disease, no response to recent systemic therapy, residual disease and an

Table 2 Patient and clinical characteristics of NET patients treated with \textsuperscript{177}Lu-DOTATATE (\(n = 279\))

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>156</td>
<td>55.9</td>
</tr>
<tr>
<td>Female</td>
<td>123</td>
<td>44.1</td>
</tr>
<tr>
<td><strong>Primary site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>104</td>
<td>37.1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>90</td>
<td>32.1</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>17</td>
<td>6.1</td>
</tr>
<tr>
<td>Large bowel</td>
<td>15</td>
<td>5.4</td>
</tr>
<tr>
<td>Unknown</td>
<td>14</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Adrenal gland</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal, not otherwise specified</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Thymus</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Cervix</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Kidney</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Ovary</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Skin</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Grade of tumour proliferation (Ki-67)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (Ki-67 &lt; 3%)</td>
<td>70</td>
<td>25.1</td>
</tr>
<tr>
<td>Medium (Ki-67 3–20%)</td>
<td>109</td>
<td>39.1</td>
</tr>
<tr>
<td>High (Ki-67 &gt; 20%)</td>
<td>23</td>
<td>8.2</td>
</tr>
<tr>
<td>Not reported</td>
<td>77</td>
<td>27.6</td>
</tr>
<tr>
<td><strong>Prior therapies for NET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>187</td>
<td>67.0</td>
</tr>
<tr>
<td>Somatostatin analogue</td>
<td>227</td>
<td>81.4</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>63</td>
<td>22.6</td>
</tr>
<tr>
<td>Targeted therapy (everolimus or sunitinib)</td>
<td>20</td>
<td>7.2</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>44</td>
<td>15.8</td>
</tr>
<tr>
<td>Liver-directed ablation or embolisation</td>
<td>60</td>
<td>21.5</td>
</tr>
<tr>
<td>Other therapy\footnote{1}</td>
<td>15</td>
<td>5.4</td>
</tr>
<tr>
<td>Disease progression at initiation of \textsuperscript{177}Lu-DOTATATE therapy</td>
<td>221</td>
<td>79.2</td>
</tr>
<tr>
<td><strong>Median age at diagnosis</strong></td>
<td>58 years (range 10–88 years)</td>
<td></td>
</tr>
<tr>
<td><strong>Median age at first \textsuperscript{177}Lu-DOTATATE cycle</strong></td>
<td>63 years (range 15–89 years)</td>
<td></td>
</tr>
</tbody>
</table>

\footnote{1}One patient was diagnosed with two primary NET, one in the pancreas and one in the small bowel. \footnote{2}Other therapies included mIBG (\textsuperscript{131}I-metaiodobenzylguanidine), peptide receptor radionuclide therapy with radioisotope labelled octreotide or octreotate and hormone therapy. NET, neuroendocrine tumour.
attempt to avoid surgery. The most common reasons for failing exclusion criteria were haemoglobin ≤ 9.0 g/dL (2.9%) and serum albumin ≤ 25 g/L (2.5%).

Implementation in January 2015 of the Lutate protocol19 led to a substantial increase in patients who met all selection criteria (60.5% of 205 patients before implementation vs 83.8% of 74 patients after implementation). More patients met suitability criteria following protocol implementation (64.4% before implementation vs 90.5% after implementation). However, fewer patients met (passed) all exclusion criteria (93.2% before implementation vs 89.2% after implementation).

Treatment

Median duration between the date of NET diagnosis and the first cycle of 177Lu-DOTATATE was 35 months (range 23 days–520 months; interquartile range 15–73 months). Overall, 204 (73.1%) patients received at least four cycles for their initial course of 177Lu-DOTATATE therapy (Supporting Information Table S1), with a median of 24 weeks (168 days) between the first and fourth cycles (range 18–52 weeks).

Twelve (4.3%) patients had not yet completed the initial course of 177Lu-DOTATATE at the time of the audit. Of the 267 patients who finished their initial course, 63 patients completed fewer than four cycles of 177Lu-DOTATATE. The most common reasons for withdrawal from therapy were death, disease progression and treatment-related SAE (Table S2).

Over half of the patients (58.1%) received concurrent radiosensitising chemotherapy with fluorouracil, capecitabine or capecitabine and temozolomide, at one or more cycles during their initial course of 177Lu-DOTATATE therapy. While radiosensitising chemotherapy was stipulated in the Lutate protocol unless contraindicated,19 its use at St George Hospital from 2014 was at the clinician’s discretion.

Outcomes

Median duration of follow up for OS and DSS was 22 months (range 0–77 months). During follow up, 117 (41.9%) patients died. Estimated median OS was 38.7 months (95% CI 33.8–51.5 months) (Fig. 1A). Cause of death was available for 113 patients. NET were the cause of death for 104 (88.9% of deaths) patients. The estimated median DSS was 49.4 months (95% CI 35.1–59.0 months) (Fig. 1B).

Median duration of follow up for all other outcomes, including disease progression, was 15 months (range 0–60 months). One hundred and three (36.9%) patients showed evidence of disease progression following 177Lu-DOTATATE treatment. The estimated median PFS was 22.9 months (95% CI 16.9–28.2 months) (Fig. 1C). Significantly lower PFS was observed in patients with non-GEP NET (median PFS 12.0 vs 24.9 months for GEP NET, \( P = 0.002 \)), and in tumours with a high Ki-67 index greater than 20% (median PFS 8.1 months vs ≥16.9 months for patients with lower or not reported Ki-67, \( P < 0.001 \)).

Toxicity

There were no deaths attributed directly to 177Lu-DOTATATE therapy and/or concomitant medications. A total of 57 treatment-related SAE was experienced by 44 patients (Table 3). Haematological, renal and hepatic treatment-related SAE were experienced by 9.7, 0.4 and 0.4% of patients respectively.

SAE were generally transient in nature with 68.4% resolving within 6 months. Unfortunately, due to a lack of follow-up data, the resolution status of 11 SAE...
(19.3%) was not known. There were six chronic treatment-related SAE that had not resolved at the date of last contact and all were haematological. Four involved neoplasms with three patients developing myelodysplastic syndrome and one patient chronic myeloid leukaemia 1–3 years after starting $^{177}$Lu-DOTATATE therapy. Other unresolved SAE included patients with lymphocytopenia and thrombocytopenia respectively.

**Sub-group analyses**

Only OS was assessed in sub-group analyses. PFS was not analysed as up-to date information for progression was not available for all patients. DSS was excluded from analysis as NET were the cause of death for most people who died and estimates for OS and DSS were similar.

GEP NET had significantly better OS than NET of other primary sites ($P = 0.013$, Fig. 2A). OS was broadly similar between midgut NET and all other GEP NET ($P = 0.293$, Fig. 2B). In the latter analysis, non-GEP NET ($n = 60$) were excluded.

Patients who met the selection criteria had an estimated median OS of 50.7 months (95% CI 34.0–61.6 months), which was significantly better than the OS in patients who did not meet all selection criteria (34.2 months, 95% CI 20.8–42.8 months, $P = 0.018$, Fig. 2C). This survival difference was largely driven by the significantly worse OS in patients who failed protocol exclusion criteria ($P < 0.001$, Fig. 2D). The effect on OS of meeting suitability criteria was not statistically significant (not shown). Eighty-six per cent of patients who failed exclusion criteria have died, with a median time to death of 14.4 months.

**Adjusted regression analyses**

Patients with a low (<3%) or medium (3–20%) Ki-67 index had 3.1 times and 2.6 times greater odds of completing treatment than patients with a high Ki-67 index (>20%) (Fig. 3A). There was some evidence that patients who failed protocol exclusion criteria and should have been excluded from treatment were less likely to complete treatment than patients who met all selection criteria (odds ratio = 0.33).

There were no significant associations between adherence to selection criteria, Ki-67 index or primary tumour site with the occurrence of treatment-related SAE (Fig. 3B).

Results from the adjusted proportional hazards regression model were consistent with the unadjusted Kaplan–Meier analysis results for OS. Patients who failed protocol exclusion criteria had significantly poorer OS than patients who met all selection criteria (HR = 4.9, Fig. 3C). Compared with patients with GEP NET, NET of other primary sites had significantly poorer OS (HR = 2.01). As expected, patients with a low Ki-67 index had significantly better OS than patients with a high Ki-67 index (HR = 0.35).

**Discussion**

Our results add to the evidence base for $^{177}$Lu-DOTATATE being a well-tolerated and promising treatment for advanced NET. Our cohort consisted of a

### Table 3 Treatment-related serious adverse events following $^{177}$Lu-DOTATATE therapy

<table>
<thead>
<tr>
<th>SAE category</th>
<th>Number of SAE</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Haematological</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bone marrow hypoplastic</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Nausea, vomiting, diarrhoea and/or abdominal pain</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Colitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
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<td>0</td>
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<td>Acidosis</td>
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<td>0</td>
</tr>
<tr>
<td>Skin infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vasovagal reaction</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Syncope and palmar-plantar erythrodysesthesia syndrome</td>
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<td>0</td>
</tr>
<tr>
<td>Neoplasm†</td>
<td>0</td>
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</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Chronic myeloid leukaemia</td>
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<td>1</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>9</td>
</tr>
</tbody>
</table>

†Neoplasms benign, malignant and unspecified (including cysts and polyps). SAE, serious adverse event.
heterogenous population with a range of ages and primary tumour sites. For patients who met all protocol selection criteria, the estimated median OS of 50.7 months was consistent with OS rates from recent large (n > 50) Australian and international studies.10–12,15,17,18,21,22 Characteristics associated with better survival were a low Ki-67 proliferation index and GEP NET primary site. The poorer OS observed for NET originating outside the gastroenteropancreatic system suggests that further evidence is required of the benefit of 177Lu-DOTATATE in the treatment of non-GEP NET.

A key finding was the significantly lower OS (median 34.2 months) in patients who did not meet all selection criteria and should have been excluded from treatment with 177Lu-DOTATATE. This was largely driven by the poor OS in patients who failed protocol exclusion criteria. It is not known if treatment with other therapies, rather than 177Lu-DOTATATE, would have improved survival in these patients. The evaluation only assessed outcomes in patients who received 177Lu-DOTATATE and conclusions cannot be drawn about the comparative effectiveness of other treatments.

The lower survival in patients who did not meet protocol selection criteria was largely responsible for the low estimated median OS of 38.7 months for the entire patient cohort. These findings provide support for, and emphasise the importance of adhering to, the selection criteria in the Lutate protocol19 for maximum treatment benefit. Reassuringly, statewide implementation in January 2015 of the protocol led to a substantial increase in the proportion of patients who met all patient selection criteria. Adherence to exclusion criteria, however, could be improved as demonstrated by the decrease from

Figure 2 Kaplan–Meier curves with 95% confidence intervals for overall survival from the start of the first cycle of 177Lu-DOTATATE treatment by primary tumour site (A,B), adherence to protocol selection criteria (C) and adherence to protocol exclusion criteria (D). (A) For all neuroendocrine tumours (NET) (n = 279), gastroenteropancreatic neuroendocrine tumours (GEP NET) were compared with all other primary sites. (B) For the GEP NET only analysis (n = 219), midgut NET were compared with all other GEP NET. The patient with two primary NET (pancreas and small bowel) was classified as a midgut NET as the small bowel primary was diagnosed first. (C,D) adherence to protocol selection and exclusion criteria were compared for all patients (n = 279). (A) Other; (■), GEP NET. (B) Midgut; (■), other GEP NET. (C) Met selection criteria; (■), failed selection criteria. (D) Met exclusion criteria; (■), failed exclusion criteria.

93.2 to 89.2% in patients meeting all exclusion criteria following protocol implementation.

The estimated median PFS of our patient cohort was lower than rates published in recent studies\(^{10-12,14,17,18,21,22}\) and could potentially be explained by differences in tumour characteristics. In general, a higher proportion of patients in this evaluation had non-GEP NET primary sites and tumours with a high Ki-67 proliferation index, which are associated with poorer PFS, than the published literature.

In our cohort, rates of treatment-related SAE were low and were similar to rates reported by other studies.
where grade 3 or 4 haematological, renal and hepatic toxicities were experienced by less than 13, 2 and 4% of patients respectively. Most treatment-related SAE were transient in nature. The development of myelodysplastic syndrome or leukaemia was uncommon and occurred in only four (1.4%) patients. Again, these rates are consistent with those reported by other large studies. Importantly, no deaths were considered to be directly caused by 177Lu-DOTATATE or concomitant medications.

The main limitation of this study was the retrospective nature of the audit. Data in medical records were collected for clinical care and not for the purpose of this analysis, which led to issues with data completeness. The reason for 177Lu-DOTATATE therapy was often not recorded and was inferred from the patient’s clinical status. Some data items required for assessing selection criteria were not well documented and patients were assumed to have met selection criteria where they were not recorded. There were also limited data available for many patients once they completed 177Lu-DOTATATE therapy and had their care transferred from the Nuclear Medicine Department. SAE may have been under-reported.

Due to the short duration of follow up, all survival estimates had wide CIs and estimates of median survival were imprecise. It is likely that rates of disease progression following 177Lu-DOTATATE therapy were underestimated and PFS overestimated, as up-to-date information for progression was not available for all patients. The interpretation of radiological scans can differ between clinicians, which may have also affected progression results. The study would have benefited from objective scoring of disease progression using Response Evaluation Criteria in Solid Tumours criteria.

Recommendations from the study have been submitted to NSW Health for consideration. Recommendations included better adherence to selection criteria, improved clinical documentation of patient assessments and treatments, objective scoring of disease progression and inclusion of outcome measures for symptom relief and quality of life.

Conclusions

Despite the limitations, this study adds further Australian evidence for 177Lu-DOTATATE being a promising treatment for advanced NET. The findings in terms of survival in patients who met all protocol selection criteria and SAE, are in keeping with studies of similar design in the published international literature. The significantly worse survival in patients who failed protocol exclusion criteria provide support for the selection criteria in the Lutate protocol and emphasise the importance of protocol adherence.

Acknowledgements

The authors thank Mr Richard Walton (Cancer Institute NSW) for his invaluable advice and assistance with the statistical analyses. The Lutate Evaluation Governance Group provided oversight and support for the evaluation.
19 Nuclear Medicine Department Lutate Services, St George and Royal North Shore Hospitals. NSW Lutate Therapy Referral and Protocol for Neuroendocrine Cancer Patients. Sydney, Australia; NSW Agency for Clinical Innovation; 2015.

Supporting Information

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

Table S1. Number of cycles, average renal dose and total activity administered during initial course of 177Lu-DOTATATE therapy (n = 279).

Table S2. Reason for withdrawal from the initial course of 177Lu-DOTATATE therapy prior to four cycles (n = 63).
Impact of universal immunohistochemistry on Lynch syndrome diagnosis in an Australian colorectal cancer cohort

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Key words
Lynch syndrome, immunohistochemistry, mismatch repair, universal screening, genetic counselling.

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Background: Current guidelines recommend a step-wise screening algorithm for all colorectal carcinomas (CRC) to identify patients with Lynch syndrome (LS).

Aim: To describe the frequencies of mismatch repair deficiency (dMMR), BRAFV600E mutations and MLH1 methylation in resected CRC, and evaluate the impact of universal screening on LS detection.

Methods: Retrospectively, 1171 consecutive cases of resected CRC were identified between 2010 and 2017 from a large multi-centre pathology service. Testing for dMMR by immunohistochemistry (IHC) was initiated by the reporting pathologist from 2010, until universal testing was introduced in 2015. Patients with dMMR were referred to the Family Cancer Clinic (FCC) for consideration of germline mutation analysis.

Results: IHC was performed on 680 tumours, with abnormal expression in 124 (18%). Referral to FCC was made for 44 of the 88 patients with abnormal IHC (excluding those with BRAFV600E mutations). Of the 29 who attended, 16 underwent germline genetic testing, and LS was diagnosed in 7 with a germline mutation. After implementation of universal testing, there was a greater incidence of dMMR (17% vs 10%, \( P = 0.02 \)), rate of BRAFV600E testing (79% vs 25%, \( P < 0.0001 \)), and referral to FCC (61% vs 33%, \( P < 0.0001 \)), but no difference in FCC attendance rate (65% vs 67%, \( P = 0.59 \)) or new LS diagnoses (1.6% vs 0%, \( P = 0.06 \)).

Conclusion: Universal IHC testing may increase the detection of LS, and should be implemented where possible. However, the full benefit was limited by low referral to and uptake of genetic testing, and further strategies are needed to overcome these barriers.

Introduction
Lynch syndrome (LS) is an autosomal dominant condition caused by a germline mutation in one of the DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6, PMS2 or EPCAM. It is the most common genetic predisposition to colorectal cancer (colorectal carcinomas (CRC)), underlying 2% to 4% of all CRC diagnoses,1 and is characterised by earlier onset and right-sided tumours with a microsatellite instability (MSI) phenotype. In addition, LS patients are at increased risk of endometrial, gastric, ovarian and several other cancers.

Screening for LS using immunohistochemistry (IHC) or MSI on the basis of age, family history or tumour histology has been shown to be inadequate2–4; studies of universal screening have found that of newly diagnosed LS cases, half are diagnosed after age 50, and almost a quarter do not meet the Amsterdam criteria or Bethesda guidelines.5 As such, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group6 and the National Comprehensive Cancer Network7 now recommend screening for LS in all individuals with newly diagnosed CRC to reduce morbidity and mortality in their relatives. A stepwise screening approach is commonly used. IHC for MMR protein expression is a cost-effective, widely accessible initial screening test for LS,3,8 with excellent reported sensitivity. However, up to 85% of MSI CRC are sporadic,9 most frequently due to acquired hypermethylation of the MLH1 promoter. Tumours with loss of MLH1 expression on IHC can be further screened for a BRAFV600E mutation or MLH1 promoter hypermethylation to exclude sporadic aetiology. Patients still suspected to have LS, where loss of expression of MMR proteins on IHC cannot be explained by a BRAFV600E mutation or MLH1 promoter hypermethylation should be referred to a genetics clinic for further evaluation and consideration of germline genetic testing.

In an attempt to identify patients with LS, our pathology service introduced pathologist-initiated MMR IHC
during 2010, and subsequent universal screening in 2015. We investigated the impact of pathologist-initiated and universal screening with MMR IHC on screening rates, LS diagnoses and rates of referral to and utilisation of the genetic counselling service in a large adult Australian cohort at a tertiary institution.

Methods

All cases of CRC that underwent bowel resection between 2010 and 2017 were obtained from the Austin Hospital pathology database in Melbourne, Australia. The Austin pathology department services a large proportion of the North East region of Victoria, including two large tertiary hospitals, a private metropolitan hospital and a regional hospital. Only pre-chemotherapy/radiotherapy resection specimens were included for analysis. Biopsies, polyps removed endoscopically and tumours with a histological type other than adenocarcinoma were not included. The results of MMR IHC were obtained retrospectively from the pathology database electronic records. The Family Cancer Centre (FCC) genetics database was then searched for all cases with an abnormal MMR IHC result.

IHC for loss of expression of the MMR proteins was performed on the Ventana BenchMark ULTRA platform, using primary antibodies against MLH1 (clone ES05, diluted 1:25; Dako, Carpinteria, CA, USA), MSH2 (clone G219-1129; Cell Marque, Rocklin, CA, USA), MSH6 (clone 44; Ventana, Tuscon, AZ, USA) and PMS2 (clone EP51, diluted 1:25; Dako). Tumours were considered to be abnormal if there was complete loss of nuclear expression of one or more MMR proteins. All cases that underwent screening from 2010 to 2012 were tested for all four proteins. In 2013, there was a shift to a two-antibody panel (PMS2 and MSH6 only), based on studies demonstrating equivalent sensitivity to the four-antibody panel. Three patients (7%) were less than 50 years of age; the median age at resection was 72 years (range 19–94). Eighty-three patients (7%) were less than 50 years of age; the majority of patients were greater than 60 years (51%).

BRAFV600E mutant protein detection was performed by IHC using the VE1 clone (Ventana), an anti-BRAFV600E monoclonal antibody, and was scored as positive if there was diffuse positive cytoplasmic staining in the tumour cells, equivalent to positive control staining, with no staining in non-tumour tissues (internal negative control). Testing for BRAFV600E mutant protein was performed for cases with loss of expression of PMS2 and/or MLH1 as part of the screening protocol. Tumours with loss of MMR protein expression and no detectable BRAFV600E mutation were recommended for referral to the familial cancer clinic service in the pathology report.

The Austin Familial Cancer Clinic (FCC) services the North East region of Victoria. Patients referred to the FCC were mailed a family history questionnaire to complete before being offered an appointment with a clinician and/or genetic counsellor. BRAFV600E mutation testing on tumour and/or germline genetic testing of the MMR genes were performed based on IHC results and family history. MLH1 promoter methylation testing was performed in cases of absent MLH1/PMS2 staining where no BRAFV600E mutation was detected. At a minimum, sequential single gene sequencing and multiplex ligation-dependent probe amplification (MLPA) were performed of the heterodimer pairs (MLH1/PMS2 or MSH2/MSH6) as directed by IHC testing. MLPA of EPCAM was performed for cases with absent MSH2 staining, except for one case which was found by sequencing to have a MSH2 gene mutation. Due to the complicating pseudogenes, long-range polymerase chain reaction (PCR) of PMS2 was also performed, as directed by IHC and methylation results. Multigene panel testing, including sequencing and MLPA for all of the LS genes, was introduced as standard in 2015. All genetic testing was performed in Australian National Association of Testing Authorities (NATA) accredited laboratories. A diagnosis of LS was made in cases where a germline MMR gene mutation was identified, and Lynch-like syndrome was diagnosed in those with mismatch repair deficiency (dMMR) on IHC, but no MLH1 promoter methylation, BRAFV600E mutation or identifiable germline mutation.

Descriptive statistics were used to analyse pathology and genetic testing results, as well as rates of FCC referral and follow up. The study was approved by the local institutional review board (LNR/18/Austin/308).

Results

Between January 2010 and December 2017, 1171 consecutive adult patients met the inclusion criteria of having undergone surgical resection of a CRC. The median age at resection was 72 years (range 19–94). Eighty-three patients (7%) were less than 50 years of age; the majority of patients were greater than 60 years (51%). Rates of MMR IHC testing and loss of expression according to age group are presented in Table 1. The rate of MMR testing was lowest in 2011 (19%) and steadily increased to 98% in 2017 (Fig. 1A). The increase in testing was greatest in the over 60 age group, while the rate of testing in the under 50 age group remained stable (Fig. 1B). The incidence of dMMR also increased (4% in 2011 vs 21% in 2017), as did the rate of BRAFV600E mutation testing in MLH1/PMS2 absent tumours (0% in 2011 vs 80% in 2017).
An abnormal staining pattern on MMR IHC was found in 124 patients (Table 2). One hundred and five (85%) patients with abnormal MMR IHC had loss of PMS2 expression. Simultaneously, loss of MLH1 was demonstrated in 86% of cases (90/105), 3% (3/105) retained MLH1 expression and no MLH1 testing was performed in 12/105 cases. Of the 105 cases with either loss of MSH6, or loss of PMS2 and a negative/unknown BRAFV600E status, 44 (50%) were referred to the FCC; 29 attended an appointment. Germline genetic testing of the MMR genes was performed in 16 (55%) of the patients who attended the FCC; BRAFV600E testing was performed in nine previously untested patients and MLH1 promoter hypermethylation testing was performed in the remaining four patients. Fifteen patients were referred to the FCC but did not attend an appointment; these patients were contacted several times through phone and post, but either declined an appointment or failed to respond (Fig. 2). There were 44 patients not referred to the FCC; the majority (91%) were over 60 years of age. Thus, in total, 59/88 patients with an abnormal IHC result did not undergo further evaluation. Five of these patients were under age 50: four had loss of expression of PMS2 on IHC with no detectable BRAFV600E mutation, and one had loss of MSH6/MSH2 expression on IHC with a strong family history of CRC. Another six patients were between 50 and 60 years of age. Loss of MSH6/MSH2 expression occurred in 8/59 patients, including one known familial adenomatous polyposis patient and one known LS patient.

A total of nine patients (1.3% of IHC tested, 0.8% of cohort) received a new diagnosis of LS or Lynch-like syndrome. The median age of resection in this group was 72 years (range 35–90). A germline mutation was identified in seven patients (four MSH6, two MSH2 and one PMS2); the other two patients had no identifiable germline mutation and were diagnosed with Lynch-like syndrome (Fig. 2). The first was a 71-year-old patient with loss of PMS2 staining, no BRAFV600E mutation and no detectable PMS2 germline mutations. The other was a 62-year-old male with loss of MSH6 and MSH2 on IHC, but no detectable germline mutation in either gene. The number of new diagnoses per year is displayed in

### Table 1

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of patients</th>
<th>MMR tested</th>
<th>MMR loss (if tested)</th>
<th>Lynch/-like syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>1171</td>
<td>680 (58%)</td>
<td>124 (18%)</td>
<td>9 (1.3%)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>83</td>
<td>81 (98%)</td>
<td>8 (10%)</td>
<td>3 (3.7%)</td>
</tr>
<tr>
<td>50–60</td>
<td>196</td>
<td>148 (76%)</td>
<td>14 (9.3%)</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>892</td>
<td>451 (51%)</td>
<td>102 (23%)</td>
<td>4 (0.9%)</td>
</tr>
</tbody>
</table>

MMR, mismatch repair.

### Table 2

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of patients</th>
<th>PMS2 loss</th>
<th>MSH6 loss</th>
<th>PMS2 loss only†</th>
<th>Referral to genetics‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BRAF mutant</td>
<td>BRAF wildtype</td>
</tr>
<tr>
<td>All</td>
<td>124</td>
<td>105 (85%)</td>
<td>19 (15%)</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>&lt;50</td>
<td>9</td>
<td>3 (33%)</td>
<td>6 (67%)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>50–60</td>
<td>13</td>
<td>7 (54%)</td>
<td>6 (46%)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>&gt;60</td>
<td>102</td>
<td>95 (93%)</td>
<td>7 (7%)</td>
<td>36</td>
<td>8</td>
</tr>
</tbody>
</table>

†BRAFV600E immunohistochemistry was performed in cases with PMS2 loss. ‡BRAFV600E mutant patients excluded from denominator.
Families of the seven patients newly diagnosed with LS were offered genetic testing resulting in two subsequent diagnoses of LS to date.

The rates of testing, MMR IHC abnormalities and LS diagnoses in the 2 years pre- and post-implementation of universal testing were compared (Table 3). Rates of MMR testing, dMMR (17% vs 10%, \(P = 0.02\)), BRAFV600E testing (79% vs 25%, \(P < 0.0001\)) and genetics referral (61% vs 33%, \(P < 0.0001\)) were significantly greater post implementation; however, FCC attendance rates (65% vs 67%, \(P = 0.59\)) and LS incidence (5/321; 1.6% vs 0/320; 0%, \(P = 0.06\)) were similar.

A subset of 206 cases from 2010 to 2014, enriched for cases with pathological features associated with LS (high-grade or mucinous differentiation), underwent retrospective analysis for MMR IHC and BRAFV600E mutation by a single gastrointestinal pathologist. Eighty-six (42%) had undergone MMR IHC testing during initial histopathological analysis. Of the remaining 120 cases, 25 (21%) had abnormal staining on IHC, of which 24/25 (96%) were over 60 years of age. All 25 cases had loss of PSM2 staining, and 21/25 were BRAFV600E mutation positive. The four BRAFV600E mutation negative cases were over 80 years of age; only one was subsequently referred to the FCC, but failed to attend any appointments. These results were not included in the results analysis of the overall cohort.

**Discussion**

In this large retrospective study of 1171 consecutive CRC, the implementation of a universal screening policy resulted in greater detection of MMR deficient tumours, but did not increase the rate of LS diagnosis. Despite higher rates of referral to the FCC and greater use of BRAFV600E mutation analysis to refine the cohort of patients referred for genetic counselling, uptake of genetic testing remained low. Several changes to our
institutions’ screening rates policy have contributed to the pattern of IHC testing rates observed in Figure 1. Recommendations from the Cancer Council Australia in 2005 included screening of all CRC cases under 50 years of age. With the initial shift from clinician-initiated to pathologist-initiated testing, this guideline was applied, which unexpectedly led to a fall in testing in 2011. Soon after, screening was expanded to patients under 70 years old, in line with the Jerusalem Guidelines, and then to all CRC in 2015.

Previous studies have reported the advantages of universal screening, including identification of up to 50% more LS-affected patients and incremental cost-effectiveness. In keeping with previous studies, our retrospective subset analysis suggests that screening based on histopathological features is unlikely to detect many more germline mutations than clinical criteria. We found that reflex IHC for MMR was feasible, with 98% of resected tumors tested in the second year of implementation. However, the clinical benefit of screening is dependent upon the downstream management of abnormal results. Rates of referral to the FCC were worryingly low, an issue not unique to our cohort. While reasons for this were not analysed in detail, in most cases, it seems that there was either a low clinical suspicion of LS or the patient declined further investigation. Barriers to referral and uptake of genetic counselling have previously been explored: possible contributions include lack of understanding of genetic syndromes and the benefits of testing, unfamiliarity with genetics services, and the burden of concurrent cancer treatment or other comorbidities.

As IHC testing for MMR and BRAFV600E mutations expanded, the proportion of appropriate referrals to the FCC also increased. However, a similar proportion of patients declined or failed to attend a FCC appointment each year, suggesting that even more cases of LS may have been missed in the later years. For example, in 2016 to 2017, there were four cases under age 50 who declined or failed to attend the FCC: one with MSH6 loss on IHC and two with loss of MSH6/MSH2. We observed a much lower overall incidence of germline mutations in our cohort (0.6%), compared to the reported incidence (2.2%) in similar cohorts. Although this was improved after introduction of universal testing (1.6%), it is still likely to be an underestimate of the true incidence.

BRAFV600E mutation testing was performed with increasing frequency during our study period; however, one-fifth of PMS2-negative tumors still did not have this tested reflexively during the last 2 years. Reflex BRAFV600E testing has been demonstrated to provide substantial time and cost savings, and would have spared nine patients in our study from requiring genetics input. Testing for the BRAFV600E mutation has been established as an important component in a cost-effective screening algorithm, and spares up to 40% of patients from unnecessary genetic testing. Commercially available monoclonal antibodies such as VE1 offer a rapid, convenient and lower cost alternative of IHC screening compared to the traditional PCR-based testing. While initial studies concluded that the sensitivity and specificity of BRAFV600E IHC was too low to be useful, subsequent studies have reported high sensitivity (96–100%) and specificity (98–100%) using automated Ventana stainers, which were used in this study. Furthermore, BRAF testing has additional predictive and prognostic utility, playing a role in predicting response to both anti-epidermal growth factor receptor (EGFR) therapies and potentially immune checkpoint inhibitors.

The role of MLH1 promoter methylation analysis is less clear, having not been well studied until recent years. During the study period, it was used in six cases to confirm sporadic aetiology where MMR IHC was abnormal but no BRAFV600E mutation was identified and the clinical suspicion of LS was low. Recent studies propose that MLH1 methylation should be used instead of BRAFV600E due to its higher specificity (78% vs 40%), and two studies have reported superior performance in terms of cost-effectiveness and efficiency compared to BRAFV600E analysis.

The strength of this study is in its large population-based cohort across several different practice settings over a period of 8 years, during which several changes to recommended LS screening protocols occurred. The testing and diagnosis rates are therefore reflective of

### Table 3

Comparison of outcomes in the 2-year periods before and after implementation of universal screening in 2015

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>320</td>
<td>321</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>MMR tested</td>
<td>170 (53%)</td>
<td>295 (92%)</td>
<td></td>
</tr>
<tr>
<td>Number of dMMR</td>
<td>33</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Incidence of dMMR</td>
<td>33/322 (10%)</td>
<td>54/321 (17%)</td>
<td>0.016*</td>
</tr>
<tr>
<td>BRAF testing in PMS2</td>
<td>8/32 (25%)</td>
<td>34/43 (79%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>PMS2 deficient</td>
<td>6/32 (19%)</td>
<td>26/43 (60%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>BRAF mutation in PMS2</td>
<td>6/32 (19%)</td>
<td>26/43 (60%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Referral to FCC†</td>
<td>9/27 (33%)</td>
<td>17/28 (61%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Attendance at FCC</td>
<td>6/9 (67%)</td>
<td>11/17 (65%)</td>
<td>0.59</td>
</tr>
<tr>
<td>New LS cases</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>LS incidence</td>
<td>0%</td>
<td>1.6%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* indicates BRAF mutant excluded. † indicates Statistically significant. dMMR, mismatch repair deficiency; FCC, Family Cancer Clinic; IHC, immunohistochemistry; LS, Lynch syndrome; MMR, mismatch repair.
real-world practice. The limitations of this study include its retrospective nature and inclusion of only a single pathology service from a single state. It is entirely possible that patients and family members may have attended other Clinical Genetics services and were therefore not captured in the FCC database. Additionally, as the true incidence of IHC abnormalities and germline mutations remains unknown, we are unable to make definitive conclusions about the effect of these policy changes.

Conclusion

Our study suggests that universal screening using MMR IHC followed by analysis for BRAFV600E mutation and/or MLH1 hypermethylation has the potential to increase the identification of patients at risk of LS, and should be implemented where possible. However, the full benefit of universal screening was limited by low uptake of genetic testing, and further strategies are needed to overcome these barriers.

References


Illicit drug use and acute kidney injury in patients admitted to hospital with rhabdomyolysis

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Key words
rhabdomyolysis, illicit drug use, acute kidney injury, renal replacement therapy, hospitalisation.

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Abstract
Background: Severe rhabdomyolysis is associated with acute kidney injury, but it is unclear if patients developing rhabdomyolysis after illicit drug use have a higher risk of acute kidney injury compared to other causes.

Aims: To provide a descriptive analysis of patients admitted with rhabdomyolysis, with a focus on illicit drug use, and to determine if illicit drug use was an independent predictor for acute kidney injury or renal replacement therapy.

Methods: We conducted a 5-year cohort study of patients admitted to Monash Health, a tertiary referral hospital network. We identified adult patients with muscle injury from ICD-10 AM codes, serum creatine kinase level greater than 1000 U/mL, and a clinical history consistent with rhabdomyolysis. We determined the prevalence and type of illicit drug involved and determined the association between illicit drug use and renal outcomes by logistic regression.

Results: Of 643 patients, illicit drug use was identified in 12%. Acute kidney injury developed in 51%, and 5% required renal replacement therapy. Compared to the rest of the cohort, patients who used illicit drugs were younger and had higher peak serum creatine kinase, and developed a higher severity of acute kidney injury. In multivariable analysis, the factors associated with acute kidney injury were illicit drug use, peak creatine kinase, cardiovascular disease, concurrent sepsis and a clinically-evident pressure injury. Chronic kidney disease and need for fasciotomy were additional risk factors for renal replacement therapy.

Conclusions: Illicit drug use was associated with acute kidney injury and renal replacement therapy independent of creatine kinase levels.

Introduction
Rhabdomyolysis is a syndrome of skeletal muscle breakdown associated with the release of potentially toxic cellular contents into the blood. It may present as an incidental finding of elevated serum creatine kinase (CK) or symptoms of myalgias, weakness and dark urine. Severe rhabdomyolysis may cause life-threatening complications like electrolyte imbalances, acute kidney injury (AKI), compartment syndrome and disseminated intravascular coagulation.1,2

An observational study of 475 patients noted that illicit drugs, alcohol and prescribed drugs were responsible for 46% of hospital admissions with rhabdomyolysis, and 65% of these patients developed AKI.3 Heroin, cocaine, cannabinoid, ecstasy (also known as MDMA) and (meth)amphetamine use have all been associated with rhabdomyolysis.3–6 Illicit drug use is a significant health issue, with 1 in 8 Australians aged 14 years and older using illegal drugs at least once over a 12-month period. The top four were cannabis, cocaine, ecstasy and (meth) amphetamines.7

Illicit drug use is also associated with AKI, often severe enough to need renal replacement therapy (RRT). The mechanism may be multifactorial, related to myoglobinuria, shock, sepsis, drug-induced malignant hyperthermia and direct nephrotoxicity. Patients who develop AKI in the setting of rhabdomyolysis have a mortality of 19% to 59%.1,4 To the best of our knowledge, there is no published Australian data on the type of illicit drugs implicated in cases of rhabdomyolysis requiring hospital admission, and there is limited data on the predictors of AKI in the setting of rhabdomyolysis and illicit drug use. We were interested to determine if illicit drug use was independently associated with the severity of AKI in patients with rhabdomyolysis.
The aims of the study were to provide a descriptive analysis of patients admitted with rhabdomyolysis, with a focus on illicit drug use, and to determine if illicit drug use was an independent predictor for AKI or RRT.

Methods

Study design, setting and patients

All adult patients (≥18 years) admitted to Monash Health acute hospitals (Monash Medical Centre, Dandenong Hospital, Casey Hospital) between 1 January 2013 and 31 December 2017 were eligible. We used the ICD-10 AM discharge diagnosis codes to identify eligible patients with rhabdomyolysis (M62.80 to M62.89 and T79.6). Three investigators systematically reviewed the electronic medical records of all patients identified from the search to confirm a clinical diagnosis of rhabdomyolysis and extract data. We excluded patients with missing CK, peak CK <1000 U/L, and CK rise due to isolated myocardial injury, such as myocardial infarction, myocarditis, or cardiac arrest. We also excluded duplicated entries arising from discharge following subsequent inpatient rehabilitation. This study was approved by the Monash Health human research and ethics committee as a quality initiative (RES-18-0000-144Q).

Outcome measures and definitions

We defined rhabdomyolysis as a CK five times above normal (>1000 U/L). We determined the peak CK as the highest CK at any time during the admission prior to RRT, including the initial CK at presentation. To assess for evidence of a rising CK, we compared the CK levels after admission with the initial CK at presentation. Patients who did not have a rising CK were deemed to have reached peak CK at presentation. The potential causes of rhabdomyolysis were grouped into non-mutually exclusive categories, recognising that some causes were multi-factorial. We determined illicit drug use status from the clinical history and toxicology results, and grouped them into non-mutually exclusive categories, as polypharmacy overdose was also common. This study defined AKI using the Kidney Disease Improving Global Outcomes (KDIGO) 2012 criteria.6 We defined chronic kidney disease (CKD) staging according to the baseline estimated glomerular filtration rate (eGFR) routinely reported by Australian laboratories using the chronic kidney disease epidemiology collaboration equation. Advanced CKD was defined as an eGFR below 30 mL/min/m² (Stage 4 or 5 CKD). We determined baseline kidney function using the strategy described by Siew et al.9 and adjudicated by a nephrologist.

Statistical analysis

We used Pearson’s correlation coefficient to determine the association between urine toxicology and clinical history of illicit drug use. We used the Mann–Whitney test to compare continuous variables between illicit drug users and non-illicit drug users; and for categorical variables, we used a Chi-squared or Fisher’s exact test. We used ordinal logistic regression to determine the factors associated with the development of AKI, and binary logistic regression to determine the factors associated with needing RRT. From the univariable analysis, we included all variables with a P < 0.25 into a multivariable model. We used a backwards elimination strategy to determine a base multivariable model, using a likelihood ratio test to compare models. A test for statistical interaction between the variables in the final model was conducted at the 1% level. We assessed model goodness-of-fit using the Hosmer-Lemeshow (binary logistic model) or Fagerland-Hosmer (ordinal logistic model) method. All analysis was performed using STATA version 15 (StataCorp, College Station, TX, USA). P < 0.05 was considered statistically significant.

Results

Patient characteristics

From the search results, we included 643 patients in the analysis (Fig. 1). The characteristics of the patients are shown in Table 1. Patients who used illicit drugs were younger than those who did not, had less comorbidities, but a higher burden of psychiatric illness. A summary of the causes of rhabdomyolysis is shown in Table 2. In some patients, more than one likely mechanism of rhabdomyolysis was identified. The median length of stay was 7 days (interquartile range (IQR), 4–13 days), of which 23.6% (151/643) required intensive care management at some point during admission (52 ventilated, 99 unventilated). Most patients were managed by general medical units (84.2%). Many patients required rehabilitation or geriatric assessment following discharge (41.6%), while 41.5% were discharged directly home and 4.4% required residential care placement.

Illicit drug use

We identified illicit drug use from the admission history in 12.3% (79/643) of patients. The categories of illicit drugs are shown in Table 3. Heroin (21/79) and meth-amphetamines (20/79) were the commonest illicit drugs used in this cohort. Urine drug screening was completed for 89/643 (13.8%) patients. A positive urine drug test
(71/89) strongly correlated with a clinical history of drug use. The best correlation was for cannabinoids ($r = 0.73$, $P < 0.001$), followed by (meth)amphetamines ($r = 0.68$, $P < 0.001$) and opioids ($r = 0.49$, $P < 0.001$). Illicit drug users were also more likely to be admitted to the intensive care unit compared to other patients ($P < 0.001$). Rhabdomyolysis Illicit drug users had a higher admission and peak CK levels than those who did not use illicit drugs ($P < 0.001$), as shown in Table 4. There was also a greater proportion of illicit drug users who experienced a rising CK after admission compared to non-illicit drug users ($P = 0.003$). The rising CK indicated that CK peaked after admission rather than before. Age and peak CK were negatively correlated ($r = -0.42$, $P < 0.001$). Compared to patients not using illicit drugs, those using illicit drugs were more likely to have hyperkalaemia ($P < 0.001$) and hyperphosphataemia ($P = 0.001$), but not hypocalcaemia ($P = 0.16$). Among the 74 patients tested for myoglobinuria, 39% were positive. For the patients who were tested, we could not detect a difference in myoglobinuria between illicit drug users and the rest of the cohort ($P = 0.12$). Myoglobinuria was not included in the subsequent regression analyses due to a high

| Table 1 Characteristics of patients by illicit drug use status ($N = 643$) |
|-----------------|-----------------|-----------------|
| Characteristic   | All patients, $n (\%)$ | Non-drug user, $n (\%)$ | Drug user, $n (\%)$ |
| Demographics     |
| Median age (IQR) (years) | 75 (53–84) | 77 (64–85) | 37 (30–47) |
| Male             | 347 (54.0) | 293 (52.0) | 54 (68.4) |
| Residential care | 8 (1.2)    | 8 (1.4)    | 0 (0.0)    |
| Comorbidities    |
| Diabetes         | 144 (22.4)  | 142 (25.2)  | 2 (2.5)    |
| Chronic lung disease | 61 (9.5)  | 58 (10.3)  | 3 (3.8)    |
| Ischaemic heart disease | 122 (19.0) | 121 (21.5) | 1 (1.3)    |
| Cerebrovascular disease | 105 (16.3) | 101 (17.9) | 4 (5.1)    |
| Peripheral vascular disease | 43 (6.7)  | 43 (7.6)  | 0 (0.0)    |
| Cancer           | 36 (5.6)    | 35 (6.2)    | 1 (1.3)    |
| Cognitive impairment | 75 (11.7) | 75 (13.3)  | 0 (0.0)    |
| Psychiatric disorder |
| Psychotic        | 39 (6.1)    | 29 (5.1)    | 10 (12.7)  |
| Anxiety/mood     | 89 (13.8)   | 57 (10.1)   | 32 (40.5)  |
| Other            | 5 (0.8)     | 4 (0.7)     | 1 (1.3)    |

IQR, interquartile range.

Table 2 Implicated causes of rhabdomyolysis ($N = 643$)

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percent of cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>48</td>
<td>7.5</td>
</tr>
<tr>
<td>Operative</td>
<td>16</td>
<td>2.5</td>
</tr>
<tr>
<td>Acute limb ischaemia</td>
<td>19</td>
<td>3.0</td>
</tr>
<tr>
<td>Pressure injury</td>
<td>468</td>
<td>72.8</td>
</tr>
<tr>
<td>Exertional</td>
<td>33</td>
<td>5.1</td>
</tr>
<tr>
<td>Seizure</td>
<td>29</td>
<td>4.5</td>
</tr>
<tr>
<td>Infection</td>
<td>36</td>
<td>5.6</td>
</tr>
<tr>
<td>Drugs and toxins</td>
<td>102</td>
<td>15.9</td>
</tr>
<tr>
<td>Myositis</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>Electrolyte disorder</td>
<td>11</td>
<td>1.7</td>
</tr>
<tr>
<td>Inherited diseases</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Thermal extremes</td>
<td>9</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Categories are not mutually exclusive.

Table 3 Categories of illicit drug use

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
<th>Percent of drug users ($N = 79$)</th>
<th>Percent of cohort ($N = 643$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>21</td>
<td>26.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>34</td>
<td>43.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Cocaine</td>
<td>3</td>
<td>8.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Meth/amphetamines</td>
<td>37</td>
<td>46.8</td>
<td>5.8</td>
</tr>
<tr>
<td>Opioids</td>
<td>40</td>
<td>50.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Other†</td>
<td>7</td>
<td>8.9</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Categories are not mutually exclusive. †Includes ecstasy (MDMA), γ-hydroxybutyrate (GHB), lysergic acid diethylamide (LSD) and N-methyl-D-aspartate (NMDA) receptor antagonists.

Rhabdomyolysis

Illicit drug users had a higher admission and peak CK levels than those who did not use illicit drugs ($P < 0.001$), as shown in Table 4. There was also a greater proportion of illicit drug users who experienced a rising CK after admission compared to non-illicit drug users ($P = 0.003$). The rising CK indicated that CK peaked after admission rather than before. Age and peak CK were negatively correlated ($r = -0.42$, $P < 0.001$). Compared to patients not using illicit drugs, those using illicit drugs were more likely to have hyperkalaemia ($P < 0.001$) and hyperphosphataemia ($P = 0.001$), but not hypocalcaemia ($P = 0.16$). Among the 74 patients tested for myoglobinuria, 39% were positive. For the patients who were tested, we could not detect a difference in myoglobinuria between illicit drug users and the rest of the cohort ($P = 0.12$). Myoglobinuria was not included in the subsequent regression analyses due to a high
number of missing observations, which were not amenable to multiple imputation. A clinically evident pressure area, fasciotomy and sepsis syndrome were similar in both illicit drug users and non-drug users. However, statin use was much lower in the illicit drug user group ($P < 0.001$).

**Acute kidney injury**

Half of the patients with rhabdomyolysis admitted to hospital experienced AKI. Illicit drug users had a greater number of patients with severe AKI compared to those who did not use illicit drugs (Table 4). Compared to patients without AKI, patients with AKI also had a longer length of hospital stay (median 6 days [IQR: 4–11 days] vs 8 days [IQR: 5–16 days], $P < 0.001$) and a greater proportion needing intensive care admission (12.5 vs 34.0%, $P < 0.001$).

The univariable logistic regression analyses are shown in Supporting Information Table S1. In the multivariable model (Table 5), the factors associated with AKI were: illicit drug use, peak CK, cardiovascular disease, sepsis and clinically evident pressure areas. There were no significant interactions between the variables examined. The model was a reasonable fit for the data (Fagerland-Hosmer, $P = 0.27$). The results of the ordinal regression model can be interpreted as proportional odds. The odds of developing a higher (more severe) stage of AKI (e.g. Stage 3 vs Stage 2, or Stage 2 vs Stage 1) are 2.8 times greater in illicit drug users than non-illicit drug

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients ($N = 643$), $n$ (%)</th>
<th>Non-drug user ($N = 564$), $n$ (%)</th>
<th>Drug user ($N = 79$), $n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial creatine kinase (U/L)†</td>
<td>2969 (1491–7891)</td>
<td>2756 (1445–6929)</td>
<td>6147 (2300–23 666)</td>
</tr>
<tr>
<td>Peak creatine kinase (U/L)†</td>
<td>4020 (1977–12 336)</td>
<td>3684 (1864–10 092)</td>
<td>12 287 (3483–28 642)</td>
</tr>
<tr>
<td>Rising creatine kinase</td>
<td>230 (35.8)</td>
<td>190 (33.7)</td>
<td>40 (50.6)</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>101 (15.8)</td>
<td>75 (13.4)</td>
<td>26 (32.9)</td>
</tr>
<tr>
<td>Hyperphosphataemia</td>
<td>125 (20.5)</td>
<td>98 (19.4)</td>
<td>27 (35.3)</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>115 (18.8)</td>
<td>96 (17.9)</td>
<td>19 (24.7)</td>
</tr>
<tr>
<td>Myoglobinuria‡</td>
<td>29 (39.2)</td>
<td>7 (58.3)</td>
<td>22 (35.5)</td>
</tr>
<tr>
<td>Chronic kidney disease status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>282 (43.9)</td>
<td>216 (38.3)</td>
<td>66 (83.5)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>3 (0.5)</td>
<td>3 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>226 (35.2)</td>
<td>215 (38.1)</td>
<td>11 (13.9)</td>
</tr>
<tr>
<td>Stage 3a</td>
<td>75 (11.7)</td>
<td>74 (13.1)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Stage 3b</td>
<td>42 (6.5)</td>
<td>41 (7.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>11 (1.7)</td>
<td>11 (2.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Stage 5 (non-dialysis)</td>
<td>2 (0.3)</td>
<td>2 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Stage 5 (dialysis)</td>
<td>2 (0.3)</td>
<td>2 (0.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Acute kidney injury severity§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>314 (48.8)</td>
<td>290 (51.4)</td>
<td>24 (30.4)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>156 (24.3)</td>
<td>144 (25.5)</td>
<td>12 (15.2)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>77 (12.0)</td>
<td>58 (10.3)</td>
<td>19 (24.0)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>96 (14.9)</td>
<td>72 (12.8)</td>
<td>24 (30.4)</td>
</tr>
<tr>
<td>Renal replacement therapy (RRT)§</td>
<td>30 (4.7)</td>
<td>22 (3.9)</td>
<td>8 (10.1)</td>
</tr>
<tr>
<td>Mean (SD) days of RRT¶</td>
<td>7.0 (5.6)</td>
<td>7.2 (5.1)</td>
<td>6.5 (7.2)</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td>96 (14.9)</td>
<td>87 (15.4)</td>
<td>9 (11.4)</td>
</tr>
<tr>
<td>Pressure area evident</td>
<td>79 (12.3)</td>
<td>69 (12.3)</td>
<td>10 (12.7)</td>
</tr>
<tr>
<td>Statin use</td>
<td>225 (35.0)</td>
<td>221 (39.2)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>Fasciotomy required</td>
<td>18 (2.8)</td>
<td>15 (2.7)</td>
<td>3 (3.8)</td>
</tr>
</tbody>
</table>

†Median (interquartile range). ‡Data only available for 74/643 (11.5%) of patients. §§Two chronic haemodialysis patients excluded. ¶One patient excluded due to uncertain duration of renal replacement therapy (hospital transfer). RRT, renal replacement therapy; SD, standard deviation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illicit drug use</td>
<td>2.8</td>
<td>1.8–4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak creatine kinase (log U/L)</td>
<td>1.3</td>
<td>1.2–1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.6</td>
<td>1.1–2.3</td>
<td>0.018</td>
</tr>
<tr>
<td>Pressure area evident</td>
<td>2.1</td>
<td>1.3–3.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3.5</td>
<td>2.4–5.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval.
users, keeping the other variables constant. For a one log increase in CK, the odds of developing a higher stage of AKI are 1.3 times greater in illicit drug users than non-illicit drug users, while the other variables are kept constant. The model can also be interpreted based on predicted probabilities, as shown for Stage 3 AKI in Figure 2 as an example, which highlighted that illicit drug use was associated with AKI independent of peak CK.

Renal replacement therapy

There were 30/641 (4.7%) patients who required RRT for AKI (Table 4). The results of the univariable logistic regression analyses are available in Table S2. In the multivariable model (Table 6), the factors associated with the need for RRT were: illicit drug use, peak CK levels, existing cardiovascular disease, advanced CKD, sepsis and need for a fasciotomy. All patients who required RRT became dialysis independent. There were no significant interactions between the variables examined. The model was a good fit for the data (Hosmer-Lemeshow, $P = 0.94$), with an area under the receiver operating curve of 0.84.

In patients with rhabdomyolysis associated with illicit drug use, the odds of needing RRT are 3.2 times higher than those not using illicit drugs on average, after adjusting for the other variables. For a one log increase in peak CK, the odds of needing RRT are increased 1.8-fold on average, after adjusting for the other variables. Patients with Stages 4–5 CKD have 8.5 times the odds of needing RRT on average, compared to those with Stages 1–3 or no CKD, after adjusting for the other variables.

Mortality

The overall inpatient mortality was 8.7% (56/643). Illicit drug users had a lower crude mortality than the rest of the cohort (1.3% vs 9.8%, $P = 0.009$). Patients with AKI also had increased mortality compared with those who did not develop AKI (12.2 vs 4.8%, $P = 0.001$).

Discussion

This study demonstrated that patients using illicit drugs had a higher severity of rhabdomyolysis, and a greater likelihood of AKI and need for RRT than patients with rhabdomyolysis who did not use illicit drugs. We also demonstrated that peak CK, clinical evidence of pressure injury, sepsis and cardiovascular disease were independently associated with higher likelihood of developing AKI. In addition to illicit drug use, peak CK, sepsis, cardiovascular disease, advanced CKD and the need for fasciotomy were also independently associated with the need for RRT.

To the best of our knowledge, this is the first analysis of rhabdomyolysis induced renal injury focused on illicit drug use in Australia. With the exception of case reports, observational studies of this nature are scarce. A Spanish study of a similar cohort of 126 patients with rhabdomyolysis requiring hospital admission, attributed rhabdomyolysis to illicit drug use in 27.8% of cases. Heroin was the most prevalent drug (24%), followed by cocaine (22.4%). The incidence of AKI and RRT was slightly higher in the Spanish study than observed in our cohort, 57.9 versus 51.2% and 9.5% versus 4.7%, respectively. The mean duration of dialysis was comparable (8.3 vs 7.0 days). Even though illicit drug use was associated with AKI in their initial analysis, the authors of the

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
Parameter & Odds ratio & 95\% CI & $P$-value \\
\hline
Illicit drug use & 3.2 & 1.1–8.9 & 0.034 \\
Peak creatine kinase (log U/L) & 1.8 & 1.3–2.4 & <0.001 \\
Cardiovascular disease & 3.8 & 1.4–9.9 & 0.009 \\
Advanced CKD & 8.5 & 1.2–58.8 & 0.048 \\
Sepsis & 6.3 & 2.7–14.7 & <0.001 \\
Required fasciotomy & 4.4 & 1.1–8.9 & 0.038 \\
\hline
\end{tabular}
\caption{Multivariable binary logistic regression for renal replacement therapy}
\end{table}
Spanish study did not include illicit drug use in their multivariable logistic regression model. Thus, our study is unique in identifying illicit drug use as an independent risk factor for AKI and RRT in patients with rhabdomyolysis.

As with previous studies, we found that CK levels were a consistent predictor of AKI. In our study, we maintained CK as a continuous variable rather than dichotomising it, and determined that peak CK was much higher in illicit drug users compared to the rest of the cohort. Illicit drug users were also much younger and presumably have a greater muscle mass which may explain this difference. However, multiple mechanisms of muscle injury may be involved with illicit drug use, including direct muscle cell toxicity, or secondary effects, such as seizure, hyperthermia, myoclonus and direct trauma from injury related to overdose. Age was a significant factor associated with AKI and RRT in univariable modelling. However, age was not significant in multivariable models as other variables in the model have accounted for the effect of age.

The most well known mechanism of renal injury from rhabdomyolysis is myoglobinuria induced vasoconstriction, obstructive tubular casts and tubular toxicity. We were unable to establish an association between myoglobinuria and AKI due to the lack of uniform testing for urinary myoglobin. However, several studies have demonstrated that serum myoglobin is a better predictor of AKI than serum CK. One study which compared CK, urine myoglobin and serum myoglobin noted that although all three markers significantly correlated with AKI, serum myoglobin had the best area under the receiver operating curve for predicting AKI. Furthermore, a systematic review found insufficient evidence for using urine myoglobin to predict AKI, and serum and urine myoglobin results can be discrepant. Urine myoglobin levels can be highly variable, as they are affected by sample collection and storage, and the method used for analysis. However, there are also potential issues for utilising serum myoglobin to assess risk for AKI. From a practical aspect, not all laboratories offer quantitative testing of serum myoglobin. Serum myoglobin peaks earlier and is cleared much quicker than CK. Thus, it is unclear if myoglobin is better than CK for predicting AKI in patients with delayed presentations.

We showed that the association between illicit drug use and AKI or RRT was independent of peak CK, which is a surrogate for the amount of muscle damaged. There may be mechanisms of renal injury from illicit drugs which are independent of myoglobinuria-induced tubular necrosis. Two recent reviews of nephrotoxicity from illicit drugs have found some evidence of direct nephrotoxicity. Where kidney biopsies have been available, renal injury other than acute tubular necrosis have included acute interstitial nephritis and glomerulonephritis as the commonest, but other findings include thrombotic microangiopathy (MDMA), vasculitis (MDMA, cocaine), vascular thrombosis or infarction (coca), and crystal nephropathy (heroin, cannabinoids). The additional mechanisms of renal injury may explain why illicit drug users develop worse AKI even allowing for their higher CK.

The main strength of our study is that we have analysed the largest Australian cohort to date, on the association between illicit drug use, rhabdomyolysis and AKI. We were also able to adjust for potential confounders for AKI and RRT in our analyses. Our study was limited by its retrospective nature, and incomplete data on myoglobinuria. Illicit drug users often used or overdosed multiple drugs, making inferences about individual drugs difficult. We lacked the ability to quantify the drug or establish their purity, and these factors may be additional confounders. We defined rhabdomyolysis using a CK cut-off of 1000 U/L (five times the upper limit of normal) as this is the method used by most researchers, and the definition adopted by clinicians in practice. Although our approach is consistent with existing literature, this CK threshold is somewhat arbitrary. However, a previous study of rhabdomyolysis which did not apply any CK cut-off showed that patients with a CK <1000 U/L did not have an increased risk for AKI in a logistic regression model.

Even though we could identify patients whose CK only peaked after admission, it may be incorrect to use the rising CK as a surrogate marker of the timing of the presentation relative to the onset of rhabdomyolysis. A rising CK may reflect the severity of injury or ongoing muscle injury, which is dependent on the mechanism of injury. For the remaining patients without a rising CK after admission, it was impossible to know if the initial CK at presentation represented the true peak or not. For some, the peak CK detected in hospital may not necessarily represent the absolute temporal peak, which could have occurred prior to presentation. Nonetheless, as a practical and parsimonious model of AKI risk, we believe that using the initial CK to represent peak CK is reasonable in the absence of a rising CK. This reflects our real-world practice based on information available to the clinician. As an observational study, we can only speculate on the timing of the presentation relative to the onset of rhabdomyolysis, and whether therapies, such as intravenous fluids may have prevented a further CK rise or reduced the severity of AKI.

Our data were derived from patients in the south-eastern, outer metropolitan area of Melbourne, Victoria.
have no reason to believe that the pattern of illicit drug use is unique to this region. The illicit drugs identified from this study is concordant with the findings of the Australian Institute of Health and Welfare survey on illicit drug use in young Australians. It is likely we can generalise our results to most cities in Australia. However, it may not necessarily reflect the pattern of illicit drug use in areas where cocaine use is more prevalent. Our study cohort was restricted to hospitalised patients, so there is a need to validate our results in non-hospitalised patients. Our findings would not be applicable to patients with CK levels below 1000 U/L.

A positive clinical history or drug screen for illicit drugs should prompt clinicians to consider rhabdomyolysis. An early diagnosis of rhabdomyolysis may reduce the risk of AKI and RRT, through meticulous fluid and electrolyte management.13,20 However, it remains unclear if fluid resuscitation alone will prevent all patients from needing RRT given the potential direct nephrotoxicity of some drugs.

**Conclusion**

Illicit drug use is associated with a higher risk of severe rhabdomyolysis, electrolyte imbalance and AKI compared to rhabdomyolysis from other causes. Prospective studies would be useful to determine the relative contributions of individual drugs to these outcomes, and whether there is a dose–response relationship.

**Acknowledgements**

The authors thank Mr Ross Major (Health Information Services, Monash Health) his for contribution to the ICD-10 search strategy.

**References**

Evaluating a risk assessment tool to improve triaging of patients to colonoscopies

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Key words
colonoscopy, risk assessment tool, simulation modelling, healthcare costs, significant bowel disease.

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Background: Colonoscopy is the gold standard in the diagnosis of significant bowel disease (SBD), including colorectal cancer, high-risk adenoma and inflammatory bowel disease. As the demand for colonoscopy services is placing significant pressure on hospital resources, new solutions are needed to manage patients more efficiently and effectively.

Aim: We investigated the impact of using a risk assessment tool (RAT) to improve selection of patients for colonoscopy procedures to detect SBD.

Methods: A hybrid simulation model was constructed to replicate the current patient triage bookings and waiting times in a large metropolitan hospital. The model used data on 327 patients who were retrospectively assessed for risk of SBD. Risk assessment incorporated blood and faecal immunochemical test results, gender and age in addition to patient symptoms. The model was calibrated over 12 months to current outcomes and was compared with the RAT and a third scenario where low-risk patients did not proceed to a colonoscopy. One-way sensitivity analyses were undertaken.

Results: Using the RAT was expected to shorten waiting times by 153 days for moderately-urgent patients and 138 days for non-urgent patients. If low-risk patients did not proceed to colonoscopy, waiting times were expected to reduce for patients with SBD by 17 days producing cost-savings of AU$373 824 through avoided colonoscopies.

Conclusions: A hybrid model that combines patient-level characteristics with hospital-level resource constraints can demonstrate improved efficiency in a hospital clinic. Further research on risk assessment is required to improve quality patient care and reduce low-value service delivery.

Introduction

In Australia, there were 778 491 colonoscopy procedures performed in the 2014/2015 financial year across both the public and private healthcare systems.1 Colonoscopy is the gold standard in diagnosis of significant bowel disease (SBD), including colorectal cancer, high-risk adenoma and inflammatory bowel disease. This is a huge burden to the health system and costs over AU$1.1 billion each year.2 Most colonoscopy services in Australia...
are performed on symptomatic patients who first present to their general practitioner (GP) for various gastrointestinal symptoms, such as abdominal pain, rectal bleeding, altered bowel habit or unexplained weight loss. Patients are then referred to specialists for further assessment. The Australian National Bowel Cancer Screening Programme screens asymptomatic Australians with a faecal occult blood immunochemical test (FIT). Patients referred through this programme represent only 4.3% of yearly colonoscopies.

The demand for both upper gastroenterology endoscopy and colonoscopy is rising steeply and is placing significant pressure on hospital resources leading to longer delays between requests for colonoscopies and appointments. Furthermore, in the symptomatic population, the symptoms that typically underpin the referral for colonoscopy have been shown to be poor predictors of SBD. The current guidelines used by Australian gastroenterologists are that every symptomatic patient referred to a gastroenterology department with a request for colonoscopy receives one with waiting times varying by perceived severity, and based on variables, including the age and gender of the patient, the constellation and duration of symptoms, the presence or absence of anaemia, and the results of a FIT test. This is complex and potentially time-consuming to follow accurately in busy clinical environments experiencing high service demands.

There is potential for risk assessment tools (RAT) to enhance the selection of patients for colonoscopy by accurately predicting SBD in patients referred to colonoscopy. Patients identified at an earlier stage of their disease have better outcomes compared with those diagnosed with later-stage disease. Evidence shows that a 12-month delay in screening patients for SBD could lead to an estimated 2.6% to 5.6% of patients with SBD developing colorectal cancer while waiting for the colonoscopy. The current practice group includes patients diagnosed under the current triaging system (Fig. 1). GP refer patients to the central processing unit requesting a colonoscopy based on patient-reported lower abdominal symptoms (e.g. rectal bleeding, altered bowel habit, abdominal pain and unexplained weight loss). Experienced gastroenterologists evaluate the referrals and triage patients into three urgency categories: Category 1 for most urgent cases, Category 2 for moderately urgent cases and Category 3 for the least urgent cases. Hospital policy dictates that patients in Category 1 are seen within 1 month, Category 2 within 3 months and Category 3 within 3–12 months. We have assumed

Current practice: The current practice group includes patients diagnosed under the current triaging system (Fig. 1). GP refer patients to the central processing unit requesting a colonoscopy based on patient-reported lower abdominal symptoms (e.g. rectal bleeding, altered bowel habit, abdominal pain and unexplained weight loss). Experienced gastroenterologists evaluate the referrals and triage patients into three urgency categories: Category 1 for most urgent cases, Category 2 for moderately urgent cases and Category 3 for the least urgent cases. Hospital policy dictates that patients in Category 1 are seen within 1 month, Category 2 within 3 months and Category 3 within 3–12 months. We have assumed
that patients were appropriately referred to a gastroenterologist by GP following guidelines.

2 Current practice plus risk tool: This scenario includes patients triaged as usual, but in addition, triaging by the consultants also incorporates a risk assessment score. The individual risk score is created by an algorithm, which considers blood test results, age, gender and FIT results. These components are entered into a computer program that calculates a positive or negative SBD prediction. Patients who are more likely to be diagnosed with SBD should be in Category 1, since an earlier diagnosis will lead to the best clinical outcomes.

3 Future practice with risk tool: This scenario triages patients based on the RAT, and withholding patients from a colonoscopy if they are diagnosed with a low risk of SBD. Previous tools have found that 60% of colonoscopies may be unnecessary. This third scenario assumed that 50% of patients in Category 2 or 3 with a negative risk of SBD did not proceed to colonoscopy. The negative health consequences of false negatives were not captured in this study.

Model structure

A discrete-event agent-based hybrid simulation model was used to simulate the three colonoscopy triaging scenarios over 12 months. Discrete-event simulation is useful for modelling system processes that include resource constraints and queuing. Agent-based models incorporate patient behaviour by giving each patient an individual identity to determine which discrete events occur within the system. The individual-level features include the components of the risk assessment score while the discrete-event features include the staff, physical and time constraints in the hospital. Figure 1 depicts the model pathway of patients being referred to the central referral processing unit. The referrals are reviewed by gastroenterology consultants and patients are assigned to an urgency category accordingly. The patients then wait, based on their urgency category, for an appointment at the colon consent clinic. Similarly, based on the urgency category, the patient is assigned an appointment time for their colonoscopy which is also influenced by the backlog of prior appointments.

Model inputs

1 Clinical inputs: Clinical inputs were derived from a pilot study where participants were recruited during their colon consent clinic appointment at a single metropolitan hospital in Queensland servicing a large area and population during 2013–2016. Complete patient data were available for 327 patients. Patients were randomly entered into the model with information, such as triage category, risk tool prediction, colonoscopy SBD diagnosis, occurrence of prior blood and FIT tests and whether the referral was a routine repeat colonoscopy. The gastroenterology department performs a maximum of 39 colonoscopies per week. The waiting times between the colon consent clinic appointment and the colonoscopy procedure were identified in the study and informed the subsequent flow of patient appointment bookings.

2 Cost inputs: The cost perspective was the public healthcare system. The cost per colonoscopy was AU$1584 based on the DRG G48C value that includes staffing, pathology and medical cost components (Table 1). The FIT and blood test costs were extracted from the Medicare Benefits Schedule (MBS) and commercial unit costs. We excluded costs for the initial GP visit and other medical costs because these were not expected to differ across the three scenarios. The currency used was 2017 AU$.

Model calibration

Using the patient throughput observed in current practice, we calibrated the model to ensure that the GP referral rate (tested between 180 and 240 patients per month) and the urgency category ‘priority value’ (which prioritises patients to move to the colon consent clinic) (tested between 3.0 and 4.0) fitted the urgency category waiting times from the
pilot study. The AnyLogic calibration tool was used with a search algorithm which minimised the difference between each urgency category’s average model waiting time and pilot study waiting time. The optimisation experiment was run over 500 iterations. The urgency category priority value was 4.0 and referral rate was 218 per month.

Analyses

The main outcomes calculated by the simulation model were overall waiting times in days (mean, SD), waiting times for patients predicted to have SBD in days (mean, SD), and hospital costs. The measures of benefit were reduced waiting times due to the RAT interventions and costs avoided. A ‘run in’ period was applied to the model for 1 year, for the model to reach stability, before measurements start to accrue. Deterministic sensitivity analyses were undertaken to test the stability of the model’s findings on several variables; the ‘clinic appointment to colonoscopy’ waiting time distribution (by urgency category), RAT sensitivity and costs (Table 1).

Results

In total, 2006 simulated patients were managed over a 12-month period (Table 2) for each scenario. For the current practice group, 58% of patients were in Category 1; 25% in Category 2; and 17% in Category 3. For the current practice plus risk tool group, Category 1 increased by

<table>
<thead>
<tr>
<th>Table 1 Model values, sensitivity values and sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent environment</strong></td>
</tr>
<tr>
<td>Coloscopies rate (max) 39 per week</td>
</tr>
<tr>
<td>GP referral to Gastroenterology unit rate 218 per month</td>
</tr>
<tr>
<td>Triage priority value (multiplier) 4.0</td>
</tr>
<tr>
<td><strong>Agent/patient characteristics in current practice, n = 327</strong></td>
</tr>
<tr>
<td>Triage category</td>
</tr>
<tr>
<td>Category 1 168 (50%)</td>
</tr>
<tr>
<td>Category 2 103 (30%)</td>
</tr>
<tr>
<td>Category 3 69 (20%)</td>
</tr>
<tr>
<td>Risk assessment tool outcome</td>
</tr>
<tr>
<td>SBD 36 (11%)</td>
</tr>
<tr>
<td>No SBD 291 (89%)</td>
</tr>
<tr>
<td>Prior blood test</td>
</tr>
<tr>
<td>Yes 133 (41%)</td>
</tr>
<tr>
<td>No 194 (59%)</td>
</tr>
<tr>
<td>Prior faecal immunochemical (stool) test</td>
</tr>
<tr>
<td>Yes 68 (21%)</td>
</tr>
<tr>
<td>No 259 (79%)</td>
</tr>
<tr>
<td>Attending for a repeat colonoscopy</td>
</tr>
<tr>
<td>Yes 95 (29%)</td>
</tr>
<tr>
<td>No 232 (71%)</td>
</tr>
<tr>
<td>Cost (AU$)</td>
</tr>
<tr>
<td>Colonoscopy procedure $1584.00 ($1346.4, $1821.6)</td>
</tr>
<tr>
<td>Blood tests $44.00 ($37.4, $50.6)</td>
</tr>
<tr>
<td>FIT test $28.25 ($24, $32.5)</td>
</tr>
<tr>
<td>Appointment booking—time from colon consent clinic to colonoscopy</td>
</tr>
<tr>
<td>Category 1—within 4 weeks 50.0% (42.5%, 57.5%)</td>
</tr>
<tr>
<td>Category 1—within 5 weeks 25.0% (28.8%, 21.3%)</td>
</tr>
<tr>
<td>Category 1—within 6 weeks 12.5% (14.4%, 10.6%)</td>
</tr>
<tr>
<td>Category 2—within 7 weeks 12.5% (14.4%, 10.6%)</td>
</tr>
<tr>
<td>Category 2—within 4 months 20.5% (23.6%, 17.4%)</td>
</tr>
<tr>
<td>Category 2—within 5 months 50.0% (42.5%, 57.5%)</td>
</tr>
<tr>
<td>Category 2—within 6 months 29.5% (33.9%, 25.1%)</td>
</tr>
<tr>
<td>Category 3—within 3 months 18.0% n/a</td>
</tr>
<tr>
<td>Category 3—within 4 months 34.0% n/a</td>
</tr>
<tr>
<td>Category 3—within 5 months 35.0% n/a</td>
</tr>
<tr>
<td>Category 3—within 6 months 13.0% n/a</td>
</tr>
</tbody>
</table>

FIT, faecal occult blood immunochemical test; MBS, Medicare Benefits Schedule; NHCDC, National Hospital Cost Data Collection; SBD, significant bowel disease.
122 patients (6.1%) and Category 2 decreased by 82 patients (4.1%). Using the RAT, patients in Category 1 diagnosed with SBD increased by 92 (11%). There were similar changes in the future practice with risk tool group.

The current practice plus risk tool scenario increased the mean waiting time by 8 days for patients in Category 1, 3 days for patients in Category 2 and 14 days for patients in Category 3. The future practice with risk tool group produced mean waiting times of 60 days for Category 1 (a 7-day decrease), 180 days for Category 2 (a 49-day decrease) and 174 days for Category 3 (a 39-day decrease). No scenario reduced the mean waiting time down to the recommended 1 month for category 1 and 3 months for category 2.

### Patients predicted to have SBD

Those more seriously affected by implementing the RAT are the patients predicted to have significant bowel disease. The risk tool predicted SBD among 140 patients in Category 1, 59 in Category 2 and 24 in Category 3. The current practice plus risk tool scenario re-categorised patients with expected SBD from Categories 2 and 3 into Category 1 shortening their waiting times by a mean of 156 and 140 days respectively. However, in doing so, it lengthened the overall waiting time for the 140 patients in Category 1 by 9 days. The benefit of the RAT was shown in the 70 patients in Category 2 and 22 patients in Category 3, who the RAT re-directed into Category 1, which were diagnosed with SBD. The future practice with risk tool enabled the removal of low-risk patients from the colonoscopy waiting list and shortened the waiting time by 7 days for patients in Category 1. This scenario estimated that 89 Category 2 patients and 39 Category 3 patients who the RAT moved to Category 1 were treated 170 days and 151 days earlier, respectively. Overall, the future practice with risk tool resulted in patients diagnosed with SBD being treated 16.7 days quicker (Table 2).

### Costs

Over 12 months, in each scenario the total cost of colonoscopies was AU$3 177 504 (95% CI: AU$2 732 653, AU$3 590 580) (Table 3). In the current practice group,

### Table 2 Number of patients and waiting times by urgency category and scenario, 12 months

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Patient #</th>
<th>Waiting time, mean (SD) days</th>
<th>Difference in waiting time</th>
<th>Patient #</th>
<th>Waiting time, mean (SD) days</th>
<th>Difference in waiting time</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current practice</td>
<td>1168</td>
<td>67.6 (12.2)</td>
<td>8 days slower</td>
<td>1290</td>
<td>75.4 (11.6)</td>
<td>7 days quicker</td>
</tr>
<tr>
<td>Current practice plus risk tool</td>
<td>1290</td>
<td>75.4 (11.6)</td>
<td></td>
<td>1310</td>
<td>60.3 (11.6)</td>
<td>7 days quicker</td>
</tr>
<tr>
<td>Future practice plus risk tool</td>
<td>1310</td>
<td>60.3 (11.6)</td>
<td></td>
<td>139</td>
<td>59.7 (11.4)</td>
<td>7 days quicker</td>
</tr>
<tr>
<td>SBD predicted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category 1</td>
<td>140</td>
<td>66.9 (11.3)</td>
<td>9 days slower</td>
<td>139</td>
<td>75.6 (12)</td>
<td>7 days quicker</td>
</tr>
<tr>
<td>Category 2</td>
<td>59</td>
<td>230.6 (40.1)</td>
<td>156 days quicker</td>
<td>89</td>
<td>60.3 (11.5)</td>
<td>170 days quicker</td>
</tr>
<tr>
<td>Category 3</td>
<td>24</td>
<td>213.5 (39.6)</td>
<td>140 days quicker</td>
<td>39</td>
<td>62.6 (10.6)</td>
<td>151 days quicker</td>
</tr>
<tr>
<td>Reduced waiting time per SBD diagnosed patient</td>
<td>2.9 days</td>
<td>2.9 days</td>
<td>16.7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SBD, significant bowel disease; SD, standard deviation.

### Table 3 Estimated hospital costs by scenario (2017 AU$)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Current practice</th>
<th>Current practice plus risk tool</th>
<th>Future practice plus risk tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy procedure costs</td>
<td>$3 177 504</td>
<td>(95% CI: $2 732 653, $3 590 580)</td>
<td>$3 177 504</td>
</tr>
<tr>
<td>Diagnostic blood tests</td>
<td>—</td>
<td></td>
<td>$54 331</td>
</tr>
<tr>
<td>Diagnostic FIT tests</td>
<td>—</td>
<td></td>
<td>$49 466</td>
</tr>
<tr>
<td>Unused diagnostic resources</td>
<td>$49 372</td>
<td>(95% CI: $42 459, $55 790)</td>
<td>$0</td>
</tr>
<tr>
<td>Avoided colonoscopy costs</td>
<td>$0</td>
<td></td>
<td>$−373 824</td>
</tr>
<tr>
<td>Total</td>
<td>$3 226 876</td>
<td>$3 268 413</td>
<td>$2 907 477</td>
</tr>
</tbody>
</table>

CI, confidence interval; FIT, faecal occult blood immunochemical test.
diagnostic tests required for the risk assessment score, but variably used to triage patients currently, cost an additional AU$49 372. The cost of implementing the risk assessment prediction was AU$90 909 over 12 months which includes the additional blood and FIT tests needed to complete the risk score. For the future practice with risk tool scenario, a total of AU$373 824 (95% CI: AU $321 489, AU$422 421) was expected to be saved in colonoscopies avoided, equating to approximately 10% of patients removed from the queue.

Sensitivity analyses
In sensitivity analyses, the influence of colonoscopy costs were tested and the annual colonoscopy costs were between $2 700 878 and $3 654 130 (Table S1). Diagnostic resource costs were between $43 308 and $58 607 due to variation in costs for blood and FIT tests. The time distributions from colon consent clinic to colonoscopy procedure varied the predicted waiting times between 61.5 and 66.2 days for Category 1 and between 221 and 229 days for Category 2 patients. The Category 1 waiting time in current practice plus risk tool scenario varied between 68 and 77 days when the number of patients with predicted SBD varied.

Discussion
Overall, implementing the RAT into routine colonoscopy triaging has the potential for patients who have SBD to be more accurately triaged and have an earlier colonoscopy. Within the current practice plus risk tool scenario, the average waiting time of patients in Category 1 increased; however, overall, patients with SBD were diagnosed 2.9 days earlier. The future practice with risk tool scenario showed that patients who have SBD could potentially have a colonoscopy 17 days quicker, while sparing many patients from an invasive procedure they will not benefit from. The current yearly cost of colonoscopy procedures in one major metropolitan hospital was AU$3.2 million. Implementing the RAT would require extra testing costs of AU$50 000 and to avoid colonoscopies unlikely to inform patient care with associated cost savings of AU$373 824.

The use of the hybrid discrete-event agent-based simulation model was an effective way to assess caseload, queuing and clinical processes in a busy gastroenterology department. Unlike Markov models or discrete event simulation, the hybrid model enabled the patient urgency categories to influence their progress through the discrete event simulation. Hospitals are complex environments and patients vary so models need to encompass multiple factors. The hybrid model embraced these elements through the booking sheet, where the specified waiting time was based on the patient’s urgency category as well as the current load of patients waiting. The value in using a hybrid model is to incorporate individual traits, which can determine health events within a constrained clinical setting, thereby creating a real-world forecast.

The growing demand of hospital colonoscopy services is widespread and effective tools that prioritise patients with potential SBD are increasingly important. The waiting times in all three scenarios still exceeded those recommended by hospital policy and reinforce the need to prioritise the diagnosis of SBD. Patient caseloads for colonoscopies are likely to be static over time, however, ruling out patients who are unlikely to benefit from colonoscopy will significantly improve care because resources can be directed to alternative, clinically effective models of care for these cases, and to further colonoscopy resources for those with a greater risk of SBD. The ethical and health related impacts of removing patients from a waiting list is a major limitation of the current study and is critical to address empirically in our upcoming trial that will evaluate the RAT. A major challenge in implementing a tool which removes patients from a waiting list is recognising that no test is perfect and introducing a robust safety net is integral. In a clinical practice setting, patients removed from a colonoscopy waiting list based upon an evidence-driven protocol will be offered an alternative care pathway provided by the specialist service together with their GP. This requires prospective study which is currently underway at our centre and collaborating institutions. In addition, a significant minority of patients make this choice themselves by deciding to cancel their colonoscopy or colonoscopy clinic appointment (and without seeking an alternative service, such as a private facility). This subgroup and their outcomes, along with the problem of early-onset colorectal cancer, requires further study.

With any diagnostic tool, consideration of false positives and false negatives is normally undertaken to assess potential harms to patients associated with inaccurate diagnoses. False negatives are potentially harmful if patients have a delayed colonoscopy in the presence of SBD and hence fail to receive prompt management. Downstream effects were out of the scope of this study, but further prospective research is underway which will capture this information. In a national screening population (asymptomatic) and depending on the patient’s gender and age, between 2.6%–5.6% of persons with advanced adenomas can advance to colorectal cancer over 12 months. Our population is symptomatic and includes conditions other than adenomas, such as
patients with irritable bowel syndrome. Thus, we expect false negatives to be lower than reported above. Harms caused by overuse of colonoscopy are adverse events (e.g., perforated bowel wall, bleeding, pain) and patient anxiety. The potential cost impact would include treatment costs of any patients with adenomas which progressed to colorectal cancer due to being omitted from the waiting list in our Scenario 3 (estimated 1 patient at $36 91415).

This study has several limitations. The exploratory cost- consequences analysis was confined by the pilot study data which limited the range of the costs and patient profiles used for the model. We excluded the potential morbidity and attendant costs attributed to any morbidity caused from delays in treating SBD patients from prolonged waiting times. Further research is required to determine if the RAT has the same accuracy outside this major metropolitan health district in Southeast Queensland. The strengths of this study are the use of a hybrid model and calibration to real world routine patient data. The model represented a complex environment and was flexible to assess alternative scenarios. We believe this study shows the RAT warrants further investigation which should include a larger trial-based study and full economic evaluation of the RAT in multiple settings.

Low-value care occurs when evidence-based recommendations suggest an intervention confers no or very little benefit to patients. In a recent report, repeat colonoscopy within 7 years has been identified as low-value ‘do-not-do’ healthcare. Colonoscopies in young people with gastrointestinal symptoms and no alarm features are also presumed to be low-value care. Although our RAT requires further evidence of benefit, it appears promising in stemming the overuse of colonoscopies in current practice partly due to the difficulties in accurately predicting SBD.

**Conclusion**

A hybrid simulation model is potentially an effective tool to demonstrate how an innovative triaging tool in a large high-demand colonoscopy service might operate more efficiently.

**References**

Elevated D-dimer levels predict adverse outcomes in hospitalised elderly patients with chronic heart failure

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1Department of Geriatric Medicine, The First Affiliated Hospital of Soochow University, Soochow, 2Heart Center, Beijing Friendship Hospital, Capital Medical University, and 3Department of Cardiology, Chinese PLA General Hospital, Beijing, and 4Department of Cardiology, Queen Mary College of Nanchang University, Nanchang, China

Abstract

Background: Elevated D-dimer levels have been associated with poor outcomes in patients with cardiovascular disease.

Aim: To study this association in elderly patients with chronic heart failure (CHF).

Methods: We analysed 1355 elderly patients who were admitted with CHF. All patients had D-dimer levels measured within the first 24 h following admission. A multivariate logistic regression model was used to assess the variables associated with chronic kidney disease. We used Cox regression analysis to assess the multivariable relationship between the D-dimer and subsequent all-cause death.

Results: In the multiple logistic regression analysis, the D-dimer was identified as a risk factor for chronic kidney disease (odds ratio = 1.278, 95% confidence interval 1.138 to 1.436, P < 0.001). The optimal cut-off level for D-dimer to predict all-cause death was found to be >885 ng/mL. In the multivariate Cox proportional-hazards model, a D-dimer level >885 ng/mL remained significantly associated with all-cause death (hazard ratio = 2.003, 95% confidence interval 1.334 to 3.010, P = 0.001). Additional analyses revealed that higher D-dimer levels were associated with an increased risk of all-cause death irrespective of the subtype of heart failure (including heart failure with reduced ejection fraction and heart failure with preserved ejection fraction).

Conclusion: In elderly patients with CHF, measurement of D-dimer levels may help to risk stratify these patients, and high D-dimer levels might be regarded as a warning sign to intensify therapy.

Introduction

Chronic heart failure (CHF), which is the end stage of most cardiovascular diseases, is highly prevalent in elderly people and is associated with high morbidity and mortality worldwide.1 The prevalence of other systemic diseases, such as chronic kidney disease (CKD), is high in patients with heart failure and increases with age.

Patients with heart failure have coagulation disorders and a risk of thromboembolic events in the vascular system.2-4 D-dimer, which is a fibrin degradation

†These authors contributed equally to this study.

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Conflict of interest: None.
product, is elevated when there is thrombus formation and/or resolution throughout the whole circulatory system, and this parameter is a biological marker of haemostatic abnormalities and thrombosis. Previous studies have shown that patients with cardiovascular disease always have higher D-dimer levels, and several studies have suggested that elevated D-dimer levels are associated with adverse events or poor outcomes in patients with heart failure. However, to date, D-dimer has not been investigated in elderly patients with CHF. In addition, previous data also suggest that CKD may be another condition, that is, associated with increased D-dimer levels. 

In this study, we aimed to investigate whether D-dimer levels measured within the first 24 h of hospital admission were associated with all-cause death in elderly patients with CHF.

Methods

Patients selection

A total of 1355 consecutive outpatients (≥ 60 years old) admitted to the Department of Cardiology, Chinese PLA General Hospital (Beijing, China), included if they had a clinical diagnosis of CHF between January 2011 and January 2014, was enrolled into the study. The diagnosis of CHF was based on standard guidelines according to the symptoms or signs, electrocardiograms, chest radiographs, and echocardiography. Patients were categorised on the basis of left ventricular ejection fraction (LVEF) as having heart failure with reduced ejection fraction (HFREF, LVEF <50%) or as having heart failure with preserved ejection fraction (HFPEF, LVEF ≥50%). Of the 1355 patients, 714 (52.7%) and 641 (47.3%) patients were included in the HFREF and HFPEF groups respectively. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². Patients had CKD with a screening eGFR based on central laboratory creatinine measurement after an overnight fast on the second day of hospitalisation. The eGFR was calculated using the Modification of Diet in Renal Disease formula. All participants had an eGFR >15 mL/min/1.73 m² and were not on dialysis or renal transplant. D-dimer levels were measured in all patients within the first 24 h following hospitalisation before the administration of any anticoagulant drugs. Electronic medical records were used to obtain the demographic variables, clinical data, laboratory values, echocardiographic parameters and information on patients’ past medical history and medications. The study was approved by the Ethical Committee for Medical Research of Chinese PLA General Hospital and was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all subjects.

Exclusion criteria

Patients with acute coronary syndrome and a previous diagnosis of acute aortic dissection, malignancy, recent (within the last month prior to admission) surgery, recent trauma or a previous diagnosis of confirmed deep vein thrombosis (DVT) and/or pulmonary thromboembolism (PTE) were excluded from the study. In order to exclude the confounders of any anticoagulant drugs so as to avoid affecting prognosis, we also removed patients with a diagnosis of DVT or PTE during the index admission. After a median follow-up period of 18 months (interquartile range of 12 to 29 months), data on all-cause death were obtained from the hospital medical records and telephone follow up.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS 19.0). All continuous variables are described as the mean ± standard deviation, and discrete variables are expressed as frequencies and percentages. The continuous variables were compared between the all-cause death and non-death groups using the Student’s t-test and the Mann–Whitney U test for variables with normal and skewed distributions respectively. The discrete variables were compared between the all-cause death and non-death groups using the Chi-square test. A Spearman correlation test was employed to study the variables related to D-dimer levels. A multivariate logistic regression model was used to assess the variables associated with CKD. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. A receiver operator characteristic curve analysis was performed to identify the optimal cut-off level for D-dimer (at which the sensitivity and specificity were maximal) for the prediction of all-cause death. Outcome curves were generated using Kaplan–Meier estimates for patients with D-dimer levels above and below the cut-off level for individual outcomes, and the groups compared with the log-rank test. We used a univariate Cox proportional hazards analysis to quantify the association of variables with all-cause death. Variables found to be statistically significant in the univariate analysis were used in a multivariate Cox proportional hazards model with a forward stepwise method in order to determine the independent prognostic factors for all-cause death. The hazard ratios (HR) with their 95% CI were recorded. The variables for which a P-value <0.1 was obtained in the univariate analysis were
considered for use in the multivariate model. A \( P \)-value of less than 0.05 was considered significant.

## Results

### Patient demographics

The clinical characteristics of the 1355 patients in the study cohort and a comparison of the baseline characteristics between patients who experienced all-cause death and those who did not are shown in Table 1. The mean D-dimer level was 1029.9 ± 1836.2 ng/mL. More male (60.2%) elderly patients with CHF were included in the study. The specific diseases leading to CHF were most frequently hypertension (74.6%) and coronary artery disease (CAD) (77.7%). Beta-blockers (74.0%), nitrates (63.8%), aspirin (77.7%) and statins (78.4%) were the main medications the patients were taking.

Patients who experienced all-cause death were more likely to be female, to have CKD, and to have lower diastolic blood pressure than those who did not. D-dimer levels, N-terminal pro-brain natriuretic peptide (NT-proBNP), creatinine and white blood cell counts were higher, and albumin, sodium and haemoglobin (Hb) levels were lower in patients who experienced all-cause death than in those who did not. More patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total cohort (( n = 1355 ))</th>
<th>Death (( n = 112 ))</th>
<th>Non-death (( n = 1243 ))</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>72.6 ± 8.0</td>
<td>73.3 ± 8.3</td>
<td>72.5 ± 8.0</td>
<td>0.287</td>
</tr>
<tr>
<td>Male (%)</td>
<td>60.2</td>
<td>48.2</td>
<td>61.3</td>
<td>0.007</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>24.8 ± 3.8</td>
<td>24.1 ± 4.2</td>
<td>24.9 ± 3.8</td>
<td>0.054</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.2 ± 20.4</td>
<td>131.7 ± 22.9</td>
<td>135.5 ± 20.2</td>
<td>0.057</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.3 ± 12.3</td>
<td>72.7 ± 12.9</td>
<td>75.5 ± 12.3</td>
<td>0.019</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>77.4 ± 15.6</td>
<td>76.7 ± 14.9</td>
<td>77.5 ± 15.7</td>
<td>0.587</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>74.6</td>
<td>67.9</td>
<td>75.2</td>
<td>0.086</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>77.7</td>
<td>80.4</td>
<td>77.5</td>
<td>0.486</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>36.1</td>
<td>36.6</td>
<td>36.0</td>
<td>0.905</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>51.1</td>
<td>42.0</td>
<td>52.0</td>
<td>0.042</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>34.4</td>
<td>55.4</td>
<td>32.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D-dimer (ng/mL)</td>
<td>1029.9 ± 1836.2</td>
<td>1801.2 ± 2868.1</td>
<td>960.4 ± 1697.7</td>
<td>0.003</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>3199.1 ± 5209.7</td>
<td>7226.4 ± 8806.8</td>
<td>2836.3 ± 4700.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total protein (g/L)</td>
<td>66.8 ± 6.2</td>
<td>66.6 ± 7.9</td>
<td>66.8 ± 6.0</td>
<td>0.803</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>39.2 ± 4.1</td>
<td>37.9 ± 4.8</td>
<td>39.3 ± 4.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.1 ± 0.6</td>
<td>1.3 ± 0.8</td>
<td>1.1 ± 0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140.6 ± 3.9</td>
<td>138.9 ± 4.8</td>
<td>140.7 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>3.9 ± 1.0</td>
<td>3.7 ± 1.1</td>
<td>3.9 ± 1.0</td>
<td>0.121</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>129.8 ± 19.8</td>
<td>121.8 ± 22.6</td>
<td>130.6 ± 19.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White blood cell (10(^9)/L)</td>
<td>6.5 ± 2.2</td>
<td>6.9 ± 2.5</td>
<td>6.4 ± 2.2</td>
<td>0.032</td>
</tr>
<tr>
<td>Platelets (10(^9)/L)</td>
<td>185.7 ± 56.5</td>
<td>184.8 ± 64.2</td>
<td>185.8 ± 55.8</td>
<td>0.866</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>48.1 ± 11.7</td>
<td>43.7 ± 12.2</td>
<td>48.5 ± 11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>41.7 ± 6.4</td>
<td>42.7 ± 7.2</td>
<td>41.6 ± 6.3</td>
<td>0.115</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>38.0 ± 9.5</td>
<td>40.5 ± 10.0</td>
<td>37.8 ± 9.4</td>
<td>0.003</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>50.9 ± 8.8</td>
<td>52.7 ± 9.3</td>
<td>50.7 ± 8.8</td>
<td>0.018</td>
</tr>
<tr>
<td>ACEI or ARB (%)</td>
<td>60.4</td>
<td>54.5</td>
<td>60.9</td>
<td>0.018</td>
</tr>
<tr>
<td>Calcium-channel blockers (%)</td>
<td>44.5</td>
<td>43.8</td>
<td>44.6</td>
<td>0.867</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>74.0</td>
<td>66.1</td>
<td>74.7</td>
<td>0.045</td>
</tr>
<tr>
<td>Other diuretics (%)</td>
<td>45.5</td>
<td>59.8</td>
<td>44.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Digoxin (%)</td>
<td>28.7</td>
<td>41.1</td>
<td>27.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Nitrates (%)</td>
<td>63.8</td>
<td>71.4</td>
<td>63.1</td>
<td>0.078</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>70.7</td>
<td>71.4</td>
<td>70.6</td>
<td>0.860</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>78.4</td>
<td>70.5</td>
<td>79.1</td>
<td>0.035</td>
</tr>
<tr>
<td>Spironolactone (%)</td>
<td>45.9</td>
<td>61.6</td>
<td>44.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>11.3 ± 8.6</td>
<td>13.2 ± 9.4</td>
<td>11.2 ± 8.5</td>
<td>0.018</td>
</tr>
<tr>
<td>NYHA heart failure class III/IV (%)</td>
<td>36.2</td>
<td>64.3</td>
<td>33.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviations (SD) or patient numbers (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.
who did not experience all-cause death were taking beta-blockers and statins. In addition, patients who experienced all-cause death had worse CHF at baseline, as indicated by a lower LVEF, a higher NYHA heart failure class (New York Heart Association heart failure class) and longer hospital stays, than those who did not.

**Spearman correlation results**

The results of the Spearman correlation test are shown in Table 2. The D-dimer level was positively correlated with heart rate, NT-proBNP, creatinine, left atrial diameter and the length of hospital stay. This measurement was also positively correlated with a history of CKD; the use of digoxin, spironolactone or other diuretics and the NYHA heart failure class. The D-dimer level was negatively correlated with systolic blood pressure, diastolic blood pressure, albumin, sodium, Hb and LVEF. The D-dimer level was also negatively correlated with the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and statins.

**Risk factors for CKD**

Variables associated with CKD were analysed using multivariate logistic regression analysis. The D-dimer level (OR: 1.278, 95% CI: 1.138–1.436, P < 0.001) was independently associated with CKD in elderly patients with CHF (Table 3). When patients were divided into HFREF and HFPEF groups, the D-dimer level was independently associated with CKD in both groups. (HFREF: OR: 1.277, 95% CI: 1.084–1.505, P = 0.003 and HFPEF: OR: 1.231, 95% CI: 1.043–1.453, P = 0.014).

**Table 2** Spearman correlation coefficients for D-dimer

<table>
<thead>
<tr>
<th></th>
<th>D-dimer</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>−0.095</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>−0.064</td>
<td>0.019</td>
</tr>
<tr>
<td>Heart rate (b.p.m.)</td>
<td>0.107</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>0.293</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>0.333</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>−0.273</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.213</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>−0.180</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>−0.231</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>−0.105</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>0.081</td>
<td>0.003</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>−0.105</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other diuretics</td>
<td>0.181</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.140</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statins</td>
<td>−0.128</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>0.166</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>0.168</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA heart failure class III/IV</td>
<td>0.214</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

**Optimal cut-off level for D-dimer to predict all-cause death**

The optimal cut-off level for D-dimer to predict all-cause death was found to be >885 ng/mL, with a specificity of 74.7% and a sensitivity of 52.7%. The area under the curve was 0.659 (95% confidence interval 0.605–0.714, P < 0.001, Fig. 1).
Prognosis of CHF

During a median follow-up period of 18 (interquartile range, 12 to 29) months, all-cause death occurred in 112 patients (8.3%). A Kaplan–Meier plot for subgroups of D-dimer levels with a threshold of 885 ng/mL is shown in Fig. 2 ($P < 0.001$). The results of the univariate and multivariate Cox proportional-hazards analyses for all-cause death of CHF patients are depicted in Table 4.

In the multivariate Cox proportional-hazards model with the forward stepwise method, a D-dimer level $>885$ ng/mL (HR = 2.003, 95% CI 1.334–3.010, $P = 0.001$), white blood cell counts (HR = 1.114, 95% CI 1.038–1.196, $P = 0.003$) and NYHA heart failure class III/IV (HR = 2.342, 95% CI 1.547–3.547, $P < 0.001$) remained associated with an increased risk of all-cause death after adjustment for variables that were found to be statistically significant in the univariate analysis. When patients were divided into HFREF and HFPEF groups, D-dimer > optimal cut-off level was also associated with an increased risk of all-cause death after adjustment for variables that were found to be statistically significant in the univariate analysis (HR = 1.788, 95% CI 1.088–2.939, $P = 0.022$ in HFREF and HR = 3.689, 95% CI 1.467–9.277, $P = 0.006$ in HFPEF).

Discussion

The results of the current study indicate that: (i) The D-dimer level was one of the important risk factors for CKD in elderly patients with CHF; (ii) A D-dimer level $>885$ ng/mL was significantly associated with all-cause death in elderly patients with CHF and (iii) Higher D-dimer levels were associated with an increased risk of all-cause death irrespective of the subtype of heart failure (HFREF and HFPEF).

We discovered that the D-dimer level was positively correlated with CKD and that it was one of the important risk factors for CKD in elderly patients with CHF irrespective of the subtype of heart failure (HFREF and HFPEF). Previous data suggest that CKD may be a condition that is associated with increased D-dimer levels, not only due to reduced elimination of D-dimers by the kidneys, but also due to activation of coagulation in patients with CKD. At the same time, dysregulation of haemostasis may also play an important pathologic role in CKD. Increasing age is known to be associated with progressively decreased renal function and increased D-dimer levels and represents another major confounding factor. Additionally, patients who experienced all-cause death were more likely to have CKD in our study; CKD has been reported to be common and an

Table 4 Univariate and multivariate analyses of all-cause death in elderly patients with chronic heart failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate HR (95% CI)</th>
<th>P-value</th>
<th>Multivariable HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer $&gt;885$ ng/mL</td>
<td>3.170 (2.187–4.594)</td>
<td>&lt;0.001</td>
<td>2.003 (1.334–3.010)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>0.604 (0.417–0.875)</td>
<td>0.008</td>
<td>0.506 (0.346–0.741)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.709 (0.477–1.054)</td>
<td>0.09</td>
<td>0.643 (0.430–0.961)</td>
<td>0.031</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>0.978 (0.970–0.987)</td>
<td>&lt;0.001</td>
<td>0.987 (0.979–0.996)</td>
<td>0.005</td>
</tr>
<tr>
<td>White blood count</td>
<td>1.078 (1.006–1.156)</td>
<td>0.034</td>
<td>1.114 (1.038–1.196)</td>
<td>0.003</td>
</tr>
<tr>
<td>NYHA heart failure class III/IV</td>
<td>3.575 (2.428–5.263)</td>
<td>&lt;0.001</td>
<td>2.342 (1.547–3.547)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted for: gender, body mass index, systolic blood pressure, diastolic blood pressure, hypertension, atrial fibrillation, chronic kidney disease, D-dimer $>885$ ng/mL, N-terminal pro-brain natriuretic peptide, albumin, creatinine, sodium, cholesterol, haemoglobin, white blood count, left ventricular ejection fraction, left atrial diameter, left ventricular end systolic diameter, left ventricular end diastolic diameter, beta-blockers, other diuretics, digoxin, statins, spironolactone, length of stay and New York Heart Association (NYHA) heart failure class. CI, confidence interval; HR, hazard ratio.
important independent predictor of death and hospitalisation in patients with heart failure.\textsuperscript{16} The co-occurrence of CKD and heart failure seems to confer an even higher rate of poor outcomes. Furthermore, the physiological relationship between CKD and heart failure is multifactorial and causally intertwined.\textsuperscript{16} Thus, a higher D-dimer level was associated with an increased risk of CKD, which may make the prognosis of heart failure worse in elderly patients with CHF.

Several studies have found an association of the D-dimer level with heart failure. However, little attention has been paid to the association of the D-dimer level with adverse outcomes in elderly patients with CHF. Higher D-dimer levels on admission have been found to be predictors of in-hospital all-cause death and 180-day all-cause death in acute decompensated heart failure patients who were hospitalised in a cardiac intensive care unit.\textsuperscript{17} Other studies have also suggested that elevated D-dimer levels were associated with long-term adverse outcomes in patients with CHF.\textsuperscript{18} In addition, D-dimer is as a fibrin degradation product; hence, it is relatively commonly used in the diagnostic tree for DVT, and even as a marker in the follow up of PTE. However, reduced cardiac function is considered an intermediate risk factor for venous thromboembolism, including DVT and PTE,\textsuperscript{19} which are associated with worse outcomes of heart failure. In our study, the D-dimer level was found to be a better predictor of all-cause death in patients with HFPEF than in patients with HFRF, partly because more patients with HFPEF also had atrial fibrillation (AF).\textsuperscript{20} In addition, an elevated D-dimer level is associated with the development of AF in hospitalised heart failure.\textsuperscript{21} Patients with concomitant heart failure and AF have a worse prognosis. However, numerous prognostic markers, such as AF, hypertension, smoking, obesity, diabetes, renal impairment, sleep apnoea and CAD and/or heart failure hospitalisation, have been identified in patients with heart failure. Although the rate of AF was lower in those who died in our study, certain prognostic factors with high hazard ratios that we did not include might affect the prognosis of heart failure when combined with those we did include in the multivariate Cox model. Thus, AF may make the prognosis of heart failure worse in the multivariate Cox model. Heart failure and AF often coexist, and each condition can promote the other, with an associated increase in overall morbidity and mortality.\textsuperscript{22}

A higher D-dimer level (>885 ng/mL) was a good marker of all-cause death in our study. It is well established that patients with CHF have systemic activation of coagulation, which may increase their risk of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{The pathophysiologic mechanism of a higher D-dimer level associated with an increased risk of all-cause death in elderly patients with chronic heart failure. It is complicated, including blood stasis, decreased activity, dilatation of cardiac chambers, reduced myocardial contractility, low cardiac output, increased intra-cardiac and central venous pressure, inflammation, neuro-hormonal activation, endothelial dysfunction, rhythm problems and renal insufficiency. Moreover, chronic kidney disease is associated with increased D-dimer levels, not only due to reduced elimination of D-dimers by the kidneys but also chronic kidney disease due to activation of coagulation in patients with chronic kidney disease. At the same time, age and dysregulation of haemostasis may also play an important pathologic role in chronic kidney disease. And the co-occurrence of chronic kidney disease and heart failure seems to confer an even higher rate of poor outcomes.}
\end{figure}
arterial and venous thromboembolic events and is associated with an adverse prognosis. These patients have elevated levels of coagulation activation markers, including fibrin D-dimer. These abnormalities can potentially be derived from many sources, such as blood stasis, decreased activity, dilatation of cardiac chambers, reduced myocardial contractility, low cardiac output, increased intra-cardiac and central venous pressure, inflammation, neuro-hormonal activation, endothelial dysfunction and rhythm problems. Therefore, the mortality among patients with high D-dimer levels might be regarded as a warning sign to intensify therapy in order to prevent adverse events. All patients with high D-dimer levels and clinical suspicion were evaluated for a possible PTE, and some had an associated diagnosis of DVT and/or PTE during the index admission and were treated accordingly. The pathophysiologic mechanism of a higher D-dimer level associated with an increased risk of all-cause death in elderly patients with CHF was shown in Fig. 3.

**Limitations**

This study has several limitations. First, it was a single-centre and observational study with a limited number of patients, so that the results should be considered as supporting the hypothesis and not possible to delineate cause and effect. Second, only baseline measurements of D-dimer levels were available. It was therefore not possible to assess changes in D-dimer levels over time and to evaluate the implications of these changes on CHF outcomes. Third, the proportion of more severe heart failure cases (NYHA heart failure class III/IV) was relatively low; thus, the results should be considered to support the hypothesis, but future systematic studies are needed to confirm these findings.

**Conclusions**

Our study demonstrated that a higher D-dimer level measured at the time of hospital admission was associated with an increased risk of all-cause death in elderly patients with CHF. We suggest that the measurement of D-dimer levels can help to risk stratify hospitalised elderly patients with CHF and high D-dimer levels might be regarded as a warning sign to intensify therapy; hence, it has strong potential to be a useful prognostic marker of CHF in the future.

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Cognitive function during exacerbations of chronic obstructive pulmonary disease

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Key words
COPD, exacerbation, hospital admission, cognitive impairment, MoCA.

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Abstract

Background: The reported prevalence of cognitive impairment in patients with stable chronic obstructive pulmonary disease (COPD) ranges 36-77%. Few studies report the prevalence of cognitive impairment in acutely unwell COPD patients.

Aims: To determine the prevalence and time course of cognitive impairment in patients with COPD during and after an admission to hospital with an exacerbation of the disease.

Methods: Patients admitted to hospital with an exacerbation of COPD between October 2013 and November 2014 were administered the Montreal Cognitive Assessment tool, COPD assessment test and modified Borg dyspnoea scale at three points in time: within 24 h of admission, between 48 and 72 h after admission and 6 weeks post discharge.

Results: Twenty-five patients agreed to participate. Four withdrew from the study after the initial evaluation. The mean (range) COPD assessment test score 24 h after admission was 26 (18–37). Cognitive impairment was found in 19/25 (76%) patients at the initial evaluation, 16/21 (76%) patients at the second evaluation. Overall, 22/25 (88%) showed cognitive impairment within 72 h of an exacerbation of COPD. Fourteen out of 21 (66%) patients showed cognitive impairment at the final evaluation. The mean Montreal Cognitive Assessment scores improved from admission (22.6) to the second evaluation (23.3) to the final evaluation 3 (24.4), but this change was not statistically significant.

Conclusion: Cognitive impairment is highly prevalent during hospital admissions with an exacerbation of COPD. This impairment does improve with time, but only a minority recover within a normal range. This will affect patients’ abilities to understand and remember information given to them in hospital and adhere to medication regimens.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive health condition that worsens over time, even with optimal treatment. COPD-associated comorbidities may also affect patients’ abilities to manage self-care tasks independently. A particular comorbidity is cognitive impairment with associated memory loss. Impairments of memory are strongly associated with functional decline and decreased quality of life. Mild cognitive impairment (MCI) is a particular condition where memory deficits are not associated with limitations of activities of daily living.

The prevalence of cognitive impairment in stable COPD has been reported in several studies. Villeneuve et al. identified MCI in 16/45 (36%) of those with COPD compared with 6/50 (12%) in a matched control group in an outpatient clinic. Grant et al. reported cognitive impairment in 77% of COPD patients with hypoxaemia, with 42% having moderate to severe cognitive impairment, compared with 14% of the control group. The cognitive impairment particularly affected tasks requiring adaptable abstract thinking as well as understanding and acting on information given.

Few studies report the prevalence of cognitive impairment in acutely unwell COPD patients. López-Torres et al. reported cognitive function in 61 COPD inpatients during and after hospital admission. Using the Montreal Cognitive Assessment (MoCA) instrument, a markedly impaired score of <20 was found in 48% of patients on...
admission; 24% of patients 9 days after admission and was also identified in 36% of patients 1 month after discharge. Some aspects of cognitive impairment did not improve with time, such as executive function, verbal learning and memory. That study did not evaluate cognitive function at more than one time point within the first 72 h of hospital admission.

In patients with COPD cognitive impairment is also associated with increased morbidity and mortality, increased length of hospital stay, increased need for supportive care after hospital discharge and an altered ability to manage activities of daily living; including inhaler management.9,10

A systematic review by Baird et al. of the effect of cognitive impairment on self-management in COPD identified seven studies reporting the association between inhaler competency and cognition. All identified studies reported both a high proportion of patients had incorrect inhaler technique and that this was strongly associated with impaired cognition.11 In addition, cognitive impairment affects patients’ ability to recognise worsening symptoms, act on these symptoms and adhere to treatment plans. Meek et al.12 report that poor accuracy of self-reported symptom intensity in patients with moderate to severe COPD was associated with even small changes in cognition.

Contributing factors to impaired cognitive function during inpatient hospital admission for an exacerbation of COPD can include dyspnoea, infection, other comorbidities, hypoxia, additional medications and an unfamiliar environment.

Overall, the practical consequences of cognitive impairment include difficulties in understanding their condition and treatment plan, inability to benefit from educational interventions such as smoking cessation, counselling or COPD self-management plans or potential failure to engage effectively in early pulmonary rehabilitation.

The aim of the study reported here was to estimate the prevalence and time course of cognitive impairment in patients within the first 72 h of admission to hospital during an exacerbation of COPD; and to further determine if cognitive impairment improved once stable.

Methods

This was a prospective cohort study. Participants were recruited from patients admitted to Hutt Hospital, an urban hospital in New Zealand (NZ). The hospital has a catchment population of 140 000 and admits approximately 340 patients with an exacerbation of COPD per year. The average length of stay (LOS) for a patient admitted with a COPD exacerbation is 3 days.

Participants

Potential participants were aged 40 years or older and admitted to hospital with a primary diagnosis of an exacerbation of COPD. Potential participants were identified by a review of daily medical service admissions to the hospital and invited to participate in the study. Although at the time of consent the study investigators were to consider that if a patient had diminished capacity, the patient’s treating medical team would be asked to determine suitability for the study, this did not arise.

Participants were excluded if they had an existing diagnosis of dementia or had other acute medical problems on admission that, in the opinion of the study investigators were likely to cause directly cognitive impairment. Participants were also excluded if they had significant communication or language problems affecting the use of the assessment instrument, or if they were living out of the hospital catchment area and unable to be assessed after discharge.

Patients enrolled in the study were evaluated at three points in time; within 24 h of admission, between 48 and 72 h after admission, either in hospital or at home if discharged, and at home 6–8 weeks after discharge when stable.

Measurements

The cognitive instrument for the study was the MoCA version 7.1; 7.2 and 7.3. Each version is equivalent and in repeat assessments alternative versions should be used to decrease possible learning effects.13 Version 7.1 was used for the initial evaluation, with version 7.2 and 7.3 used on subsequent evaluations.

The MoCA is a screening tool that detects MCI and has an administration time of 10 minutes. It tests multiple cognitive domains, including visuospatial and executive functioning, memory and attention. It is validated to detect MCI³ and is also validated in COPD patients.⁶ Cognitive impairment is likely to be present if the score is <26/30.

Repeated cognitive testing has been studied³ and in stable patients the mean (SD) change between two evaluations is 0.9 (2.5) points. To take account of educational background one point is added to the MoCA score for those with 12 years of education or less.¹¹

Exploring potential causes for cognitive impairment

Although participants with a known other cause of cognitive impairment were not recruited for this study, other information was collected to determine
associations with cognitive impairment that were potentially causal. These were collected using a standardised data collection form from hospital medical records. Demographic data, smoking status, LOS, use of noninvasive ventilation or intensive care admission, number of medications, number of comorbidities, oxygen saturation on admission to hospital and partial pressures of oxygen and carbon dioxide were recorded. The most recent spirometry performed in the stable state up to 5 years before the hospital admission was accepted as a measure of baseline lung function.

The COPD assessment test (CAT) was used to assess COPD-related quality of life. This is a short self-administered questionnaire. The eight items in the questionnaire cover a range of symptoms including cough, phlegm, chest tightness, breathlessness, activity limitation, confidence, sleep and energy, to assess the disease severity and are graded by the patient from 0 to 4. A total score below 10 suggests low impact of the disease, with a score between 11 and 20 suggesting moderate impact and scores over 21 suggest high impact of the disease. The CAT was completed at each study visit.

The modified Borg and Modified Medical Research Council (MMRC) dyspnoea scales were used to assess breathlessness at each study visit.

### Statistical analysis

The sample size calculation was based on the difference in mean MoCA scores between the first and third visit. A minimum clinically important difference of two points was used to detect change for the MoCA. To estimate this difference between two time points with 80% power, with a type I error rate of 5%, a sample size of 19 participants was needed, and we aimed to recruit 25 patients to allow for attrition.

Data were entered into a spreadsheet, and data analyses were completed using the data analysis functions in Excel using t-tests and a correlation coefficient estimation.

Ethical approval was granted by the hospital where the study was undertaken and the Central Regional Ethics committee NZ reference 13/CEN/85.

### Results

A total of 25 patients consented to participate, and of these all were considered by the study investigators to have sufficient capacity to consent to the study. Four withdrew from the study during the acute phase assessments. Table 1 describes the baseline characteristics of the patients. Men comprised 13/25 (52%) of the group, and the mean (range) age was 69 (50–83) years. Most patients, i.e. 17/25 (68%), were of European descent, with 7/25 (28%) Māori (indigenous people of NZ) and 1/25 of Pacific ethnicity. All patients had an established diagnosis of COPD with a mean (range) FEV1 0.87 (0.4–2.46) L. Severe or very severe airflow obstruction was documented in 22/25 (88%) patients. There were eight current smokers, one never smoker and 16 ex-smokers. The mean tobacco smoke exposure was 44 pack-years. Patients had a high number of comorbidities, and a mean (range) of 8 (2–15) prescribed medications. Five (20%) patients required noninvasive ventilation, and four (16%) patients required treatment in the intensive care unit of the hospital. The average (range) LOS was 3.8 (1–18) days with 12 (48%) patients discharged after 1 day, and 18 (72%) discharged within 72 h of admission.

Table 2 describes the relevant clinical data and assessment tests. The respiratory rate and oxygen saturations were similar over the three study visits. Of the 25 patients assessed at the first assessment, eight (32%) patients received supplementary oxygen therapy, 4/21 (19%) at the second assessment and 3/21 (14%) were on domiciliary oxygen therapy at the final visit 6–8 weeks after discharge. Eighteen (72%) patients had either a venous (2/18) or arterial blood gas (16/18) performed on presentation to the emergency department. Excluding the venous samples, the mean (range) PaO2 was 78.3 mmHg (34–227), and the mean (range) PaCO2 was 57.4 mmHg (35–90).

The Borg scale for dyspnoea, the CAT and MoCA scores all improved from the initial evaluation to the evaluation 6–8 weeks after discharge. The mean (range) CAT score was 26 (18–37) on admission and 20.4 (7–35) 6–8 weeks after discharge; mean paired difference (95% confidence interval (CI)) −5.3 (−7.7 to −2.9), P < 0.001.

### Table 1 Patient characteristics (N = 25)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Māori</td>
<td>7 (28)</td>
</tr>
<tr>
<td><strong>GOLD category of severity</strong></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Severe</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Very severe</td>
<td>11 (44)</td>
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</table>

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.4 (8.7)</td>
<td>70 (63–73)</td>
</tr>
<tr>
<td>Smoking status (pack-years)</td>
<td>44.2 (25.6)</td>
<td>40 (37–50)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>0.87 (0.45)</td>
<td>0.68 (0.56–1.08)</td>
</tr>
<tr>
<td>Comorbidities (N)</td>
<td>4 (2.4)</td>
<td>4 (1–6)</td>
</tr>
<tr>
<td>Usual prescribed medicines (N)</td>
<td>8 (3.8)</td>
<td>8 (5–11)</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>3.8 (4.5)</td>
<td>2 (1–4)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.
The MMRC score was recorded in 15/25 (60%) patients at the initial assessment and in 13/21 (62%) at the final assessment. The mean (range) MMRC score was 4.5 (3–5) at the initial assessment and 3.6 (2–5) at the final assessment. Cognitive impairment, defined as a MoCA score less than 26/30, was found in 19/25 (76%) patients on admission, 16/21 (76%) patients at the second study visit between 48 and 72 h after admission and in 14/21 (66%) patients at the final study visit 6–8 weeks after discharge. Overall, 22/25 (88%) showed cognitive impairment within 72 h of admission to hospital. The mean MoCA scores improved from admission (22.6) to study visit two (23.3) to study visit three (24.4), but this change was not statistically significant. The paired difference (95% CI) between the third and first evaluation was 1.5 (−0.04 to 3.0), \( P = 0.055 \). There was a statistically significant improvement from the worst MoCA during the acute phase of the illness (within 72 h of admission to hospital) and MoCA during stable COPD, mean (95% CI); 2.1 (0.3–3.9), illustrated in Figure 1. The four who withdrew from the study during the acute phase assessments were systematically different at the final unobserved assessment, the point estimates could have been different.

In this study, there were no statistically significant associations between the MoCA score and oxygen saturation levels, breathlessness or disease severity. There was weak evidence that a greater number of comorbidities was associated with greater cognitive impairment (correlation coefficient = −0.39, \( P = 0.05 \)), as shown in Figure 2.

**Discussion**

Cognitive impairment was highly prevalent during an exacerbation of COPD with a substantial majority of patients having an abnormal MoCA score during the first 3 days of an exacerbation of COPD. Although MoCA scores improved during admission, this improvement was small and not statistically significant. Only a minority of patients improved to have a MoCA score within the normal range once stable. The variability in MoCA scores, paired standard deviations of between 3.2 and 3.8, were larger than that anticipated in our sample size calculation, and so the study is likely to be underpowered to detect important differences in the MoCA scores, with wide confidence intervals for our estimated differences. In addition, if the four patients who withdrew from the study during the acute phase assessments were systematically different at the final unobserved assessment, the point estimates could have been different.

**Table 2** Clinical data and assessment tests

<table>
<thead>
<tr>
<th></th>
<th>Study visit 1 (on admission)</th>
<th>Study visit 2 (24–72 h)</th>
<th>Study visit 3 (6–8 weeks post discharge)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( N = 25 )</td>
<td>( N = 21 )</td>
<td>( N = 21 )</td>
</tr>
<tr>
<td>Respiratory rate (per min)</td>
<td>20.5 (3.7)</td>
<td>21.2 (3.3)</td>
<td>20.5 (4)</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>93.3 (2.5)</td>
<td>92.9 (3.8)</td>
<td>94.5 (2.1)</td>
</tr>
<tr>
<td>Borg</td>
<td>3.7 [1.9]</td>
<td>3.0 [2.0]</td>
<td>2.1 (1.3)</td>
</tr>
<tr>
<td>MoCA</td>
<td>22.2 [3.9]</td>
<td>23.3 [4.4]</td>
<td>24.4 (3.2)</td>
</tr>
</tbody>
</table>

CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; MoCA, Montreal Cognitive Assessment.

**Figure 1** Box plot of MoCA scores study visit 1 and 2 compared with study visit 3. MoCA, Montreal Cognitive Assessment.

**Figure 2** The association of MoCA scores at study visit 1 and number of comorbidities with linear regression line. MoCA, Montreal Cognitive Assessment.
Cognitive function in COPD exacerbations

The finding that cognitive impairment improves after a hospital admission is concordant with the results reported by López-Torres et al. In that study, the prevalence of cognitive impairment during the hospital admission was reported as 48%, much less than the 88% we observed. This difference may be explained by the differing MoCA score cut-offs used to define cognitive impairment, 20 versus 26, and by the use of single versus multiple observations.

Our study found that cognitive impairment was very common and more prevalent than reported in other studies. This finding may be due to the severity of disease, as this has been reported previously, as the majority of patients in our study had severe to very severe COPD.

There was an improvement in CAT scores from acute phase of the exacerbation to stable COPD that was statistically significant as might be expected when an acute illness is treated successfully. Although the majority of patients recorded a moderate to high impact of the disease during the acute and stable phase, there was a greater number of patients with moderate impact of the disease in the stable COPD.

We did not identify any statistically significant associations with disease severity, oxygen saturation levels or breathlessness. However, we did find that there was some evidence to suggest that a greater number of comorbid conditions was associated with an increase in cognitive impairment. A larger study may provide more insights into the prevalence of the various potential mechanisms that may cause cognitive impairment.

The patients in our study were representative of COPD patients that are admitted to our secondary care level hospital with the majority of patients of NZ European ethnicity, and 28% of our study population identifying as Māori. The age, gender and smoking status are similar to that reported in two NZ audits of COPD admissions. For our population group, the LOS was shorter than has been reported previously in NZ. This is most likely in part because our hospital is in an urban region of NZ, these hospitals were found to have lower LOS than rural regions, and in addition our hospital provides COPD patients with supportive care post discharge enabling early discharge.

Cognitive impairment is an important comorbidity to consider as it may make the ongoing self-management of COPD more challenging, especially in those with multiple comorbid health conditions. In particular cognitive impairment may affect patients' ability to understand and remember information given to them in hospital. Medication regimens for the treatment of COPD can be complex often requiring more than one medicine taken at varying time periods during a day. In addition patients are often prescribed different inhaler devices each requiring a specific inhalation technique and are technically challenging to administer. Further complexities are added by health professionals who provide inconsistent messages when involved in teaching inhaler technique, as they themselves are known to have poor knowledge and ability to use the different inhaler devices. In addition treatment regimens often change on discharge from hospital requiring the patient to acquire and remember new information.

Verbal memory, learning and problem solving functions are the cognitive domains that are more frequently impaired in patients with COPD. Therefore, cognitive impairment may also impact on the patient’s ability to problem solve, manage and adhere to their medication regimen, recognise deterioration and act on their treatment plans.

Even in the absence of direct controlled trial evidence of interventions that enhance adherence to treatment plans, it is important that health professionals ensure that there are sufficient strategies in place to support safe discharge and greater treatment adherence in those with COPD and cognitive impairment.

**Conclusion**

Cognitive impairment in COPD is common and highly prevalent during an acute exacerbation. It does not fully resolve after the acute phase of the illness has passed. This needs to be considered for effective and safe discharge planning, when providing patient education and advice, pulmonary rehabilitation and ongoing long-term management. As this study was underpowered, further research examining the prevalence of cognitive impairment and interventions to improve treatment adherence is warranted.

**Acknowledgements**

The authors acknowledge Ms Kirsten Lassey and Mr Alan Shaw (Hutt Valley District Health Board) for their contribution to data collection.

**References**


BRIEF COMMUNICATIONS

Analysis of patients referred for aged care assessment with concerns related to hoarding or squalor

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Key words
cognitive dysfunction, domestic squalor, geriatrics, health services for the aged, hoarding.

Abstract

Patients referred with concerns related to hoarding and squalor frequently pose significant management challenges. We conducted a retrospective analysis of 120 patients referred to an Aged Care Assessment Service. The hoarding only group comprised 27%, squalor only 15% and hoarding and squalor 53%. Mild cognitive impairment was the most common cognitive diagnosis, no cognitive diagnosis was made in 25% and the usual diagnostic process could not be followed in 13%. This analysis provides relevant Australian specific data to assist with planning service delivery for a group of patients with complex management issues.

Patients referred with concerns due to their living environment commonly have issues related to hoarding and squalor. Hoarding is defined as the accumulation of a vast amount of possessions which compromises living spaces and causes impairment in social and occupational functioning. Hoarding can occur in a variety of medical and psychiatric conditions and is associated with executive dysfunction. It can also occur as a distinct entity, hoarding disorder, where a patient experiences persistent difficulty with discarding possessions regardless of the value. The mean age of patients diagnosed with hoarding disorder is between 53.2 and 66.9 years.2,4

Squalor is defined as a living environment that is ‘so unclean, messy and unhygienic that people of similar culture and background would consider extensive clearing and cleaning to be essential’.5 It is not recognised as a distinct diagnostic entity in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition and presents as an epiphenomenon alongside other diagnoses. Similar to hoarding, it takes many years before squalor becomes clinically apparent with 72.3 years being the mean age of diagnosis.6

Squalor can occur with or without hoarding. A study by Lee et al.7 found that patients who live in squalor without hoarding tended to be younger (mean age 69.9 years). Patients who misuse alcohol, comprising 47% of those living in squalor less than 65 years old, were less likely to hoard.9 The environment inhabited by people with hoarding behaviours can deteriorate into squalor if extensive clutter impedes cleaning efforts. They tend to present at a later age (mean age 75.8 years), usually due to loss of a domestic partner, onset of frailty or neurocognitive disorders.7

An understanding of the underlying aetiology is important to inform management. For instance, the treatment of a patient with hoarding disorder is different from someone with stereotypic hoarding associated with frontotemporal dementia. Multidisciplinary teams, such as the Aged Care Assessment Service (ACAS) were well suited to the assessment and initial management of these patients, but this is no longer feasible due to reorganisation and funding changes of the ACAS model through My Aged Care. At present, it remains unclear which publicly funded community-based health service should be responsible.

We present a descriptive analysis of the demographic and medical characteristics of hoarding and squalor patients referred to Western ACAS for the purpose of planning future service delivery. Western ACAS serves five local government areas in western Melbourne. Four out of the five local government areas are socioeconomically disadvantaged based on census data.10 All patients referred to ACAS during the analysis time frame, between 2009 and 2015, with issues related to hoarding or squalor were included. Referral source, demographic
data and medical diagnoses were collected. Cognitive diagnoses were either confirmed by an ACAS geriatrician or resulted from referral to the local Cognitive Dementia and Memory Service (CDAMS). Ethics approval was obtained from the low-risk ethics committee.

In total, 120 patients were included in the analysis. The total number of referrals to ACAS, where face-to-face contact was made for initial assessment, was 23,358 during the analysis timeframe. Hoarding and squalor patients represent a small (0.005%) numerical proportion of the total referral base. The hoarding only group comprised 32 of 120 (27%), squalor only comprised 18 of 120 (15%) and hoarding and squalor comprised 64 of 120 (53%). There was insufficient information to determine the category for 6 of 120 (5%).

The most common referral source was inpatient social workers across the related health network, with 30 of 120 (25%) of referrals being generated in this manner. Home and community care services referred 17 of 120 (14%), relatives and neighbours referred 16 of 120 (13%) and general practitioners referred 13 of 120 (11%). Five patients referred themselves 5 of 120 (4%).

The characteristics of the patients are presented in Table 1. Gender was evenly distributed (females were 61/120 or 51%) and over half of the patients (72/120 or 60%) were born in Australia. The second most common geographical region of birth was Europe with 42 of 120 patients (35%). In keeping with the geographical origin of birth, English was the most common primary language spoken (97/120 or 81%) and Western European languages made up a majority of the remaining primary languages. Educational achievement was available for 62 patients. A total of 29 of 62 (47%) completed secondary schooling and 9 of 62 (8%) completed a tertiary qualification. A significant majority of patients (104/120 or 87%) were reliant on the aged pension as their sole income source.

The average Mini Mental State Examination (MMSE) score 24 of 30 but scores were available for 55 of 120 (46%) patients. The low MMSE rate and insufficiently followed diagnostic process to characterise cognition (15/120, 13%) were a result of either patient refusal to engage with cognitive testing or ACAS clinicians’ reluctance to pursue a diagnosis, and instead choosing to focus on the environmental consequences. Of the 105 patients who underwent cognitive testing, the most common cognitive diagnosis was mild cognitive impairment (MCI) (31/105 or 30%) with almost all related to underlying vascular aetiology (30/105 or 29%). No diagnoses relevant to cognition were made in 26 of 105 (25%) patients.

All potentially relevant diagnoses that were made are included in Table 2 below. A minority of patients had more than one relevant diagnosis, resulting in the total number exceeding 105 and the percentage total exceeding 100%. Hypertension (57/120, 48%) and mental health disorders, not further sub-typed (57/120, 48%), were the most common comorbidities.

**Discussion**

In this retrospective analysis, half of the patients had mixed hoarding and squalor and over a quarter with hoarding only. Most were born in Australia and a significant proportion receives a pension. Hypertension and
mental health disorders were comorbid conditions in approximately half of the cohort. Two-thirds of patients had cognitive diagnoses related to psychiatric disorders or impairment due to vascular aetiology including MCI and vascular dementia.

Given that this is essentially a convenience sample, it is likely that the proportion of patients referred to the ACAS (0.005% of total referrals) significantly underrepresents the scale of the problem even amongst the referral pool. Further, the number of referrals cannot be used to extrapolate community-based prevalence figures due to the multitude of other potential referral destinations, such as the Aged Psychiatry Assessment and Treatment Team (APATT), and the likelihood that patients may not come to the attention of public health or social services until conditions are severe. Interestingly, the APATT only referred a single patient, despite psychiatric comorbidities being present in up to 50% of patients including in our sample.

ACAS is primarily considered to be a health service, at least historically. As a result, many squalid households are likely not referred as they are perceived not to be a health problem. In the authors’ experience, referrals for patients with concerns regarding self-neglect rather than hoarding or squalor are more likely to be referred to and accepted by the ACAS. ACAS is also primarily an aged person service and does not universally accept younger patients; therefore, younger patients living with hoarding or squalor may be left without an appropriate referral destination.

This case series was made up of community dwelling individuals referred to a community-based service; however, the highest proportion of referrals was generated by inpatient social workers. Even then, inpatient clinicians tend to underreport potentially significant hoarding or squalor unless it is immediately relevant to the discharge planning process. People who live in squalor and hoarding often demonstrate a lack of concern for housing conditions, reduced socialisation and repeated refusal of assistance. They can lack the motivation and initiative required to improve their physical circumstances, which can lead to prolonged exposure to heightened environmental risks, disproportionate rates of illness and premature mortality. Most of this cohort had cognitive diagnoses that could potentially affect executive function, which highlights the need to use screening tests that more adequately test frontal executive function instead of being overly reliant on the MMSE. The importance of expert assessment and case management of patients with hoarding and squalor issues within a multidisciplinary team cannot be overstated. The inpatient setting may provide immediate access to those essential multidisciplinary assessments, including neuropsychological testing, but the protracted nature of attempts to assess and manage the causes and environmental consequences of hoarding and squalor means utilising inpatient services is often not viable.

Our analysis provides relevant Australian specific data on this complex cohort of patients, which is characterised by significant rates of cognitive impairment and often challenging social circumstances, to assist in planning future service delivery and optimising current in-hospital and community-based care.

Acknowledgements

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References


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Idarucizumab for dabigatran reversal: the first 6 months in a tertiary centre

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Key words idarucizumab, dabigatran, reversal, safety, use.

Abstract

This retrospective audit reviews patients on dabigatran presenting with bleeding or requiring urgent surgery in the Wellington region, whether they received idarucizumab appropriately and the outcome of episodes. Eighty patients were identified with bleeding or need for urgent surgery, 14 of which received idarucizumab. In patients who received idarucizumab, use was safe, effective and overall appropriate. Idarucizumab was underutilised with patients who could have benefited not receiving it; however, some patients who were treated may not have required it. Increased awareness and use may improve outcomes.

Dabigatran (Pradaxa) is a direct thrombin inhibitor listed on the Pharmaceutical Schedule in New Zealand in July 2011.1,2 In the setting of uncomplicated atrial fibrillation non-vitamin-K-antagonist oral anticoagulants (NOAC) such as dabigatran are now preferred to warfarin for eligible patients.3 NOAC have 10% lower mortality and approximately 50% lower risk of intracranial haemorrhage or haemorrhagic stroke compared to warfarin.4,5 Despite these encouraging findings, there was an ongoing desire for an effective reversal agent. As of 1 September 2016, idarucizumab was listed on the New Zealand Pharmaceutical Schedule. It is a monoclonal antibody with a humanised fragment antigen binding site that binds specifically to dabigatran with 350x higher affinity than dabigatran to thrombin.5 The Wellington regional district health boards (Capital and Coast, Hutt Valley and Wairarapa) created a guideline for the use of idarucizumab (Figure 1). This included the requirement that a thrombin time (TT) was done to confirm the presence of dabigatran prior to the use of idarucizumab based on the interim analysis by Pollack et al.6

This retrospective audit reviews the management of patients on dabigatran presenting with major bleeding or requiring urgent surgery, idarucizumab use and outcome of events. New Zealand is unique, in that dabigatran was the only publicly funded NOAC at the time of this audit.

As the local protocol (Fig. 1) requires a TT pre-dosing, therefore a search of the laboratory electronic database was performed for all TT requested in the Wellington region in the first 6 months after idarucizumab was available (1 September 2016 to 28 February 2017). All analysed samples were included. An electronic notes review was undertaken to identify those on dabigatran with either bleeding requiring admission to hospital or urgent surgery or other invasive procedures that should not be delayed for at least 8 h for which normal haemostasis was required. This approach was used as it was found that coding of surgical and bleeding events often did not include dabigatran use. Bleeding was classified according to the International Society of Thrombosis and Haemostasis criteria.7 Notes were examined for any complications of dabigatran and/or idarucizumab, if a follow-up TT was performed and how re-introduction of anticoagulation was managed. As there

Funding: None.

Conflict of interest: None.
is no current specific prospective or retrospective evidence on what would be considered an appropriate resumption rate of anticoagulation with dabigatran, for this audit, we have considered the original article from Pollack et al.\(^8\) as our standard.

The Wellington region does not have on site access to dabigatran levels and does not use a dilute TT. As the TT is so sensitive to dabigatran concentrations, local experience has led us to consider those with a TT $\geq 60$ s as ‘therapeutic’ and those $<60$ s as ‘non-therapeutic’ in the context of the bleeding patient (normal TT; $<21$ s). It is not used to dose dabigatran.

Prospective records of idarucizumab dispensing were requested from the New Zealand Blood Service and local hospital pharmacies and matched to those found from TT. This was also used to identify if the pre-dosing TT was performed as per protocol.

This project, being a retrospective audit of a clinical policy with no identifying patient details included, was granted ethics approval by the Capital Coast Health Audit Committee prior to the commencement and collection of data.

A total of 2381 TT was performed in the 6-month study period corresponding to 1254 patients. Eighty patients were identified who were on dabigatran who presented with bleeding or needing urgent surgery. Fourteen received idarucizumab (Table 1). Outcome data were found on all patients.

Fifty-one patients presented with bleeding (Table 1). Twenty-one patients had major bleeding, of which 11 (21.6%) patients received idarucizumab (five for gastrointestinal bleeding, five for intracranial bleeding and one for a splenic laceration). Two (4%) patients died within 30 days of bleeding from their presenting complaint (one

Figure 1 Local guideline for use of idarucizumab. Management should be individualised according to the severity and location of the haemorrhage.
haemorrhagic stroke and one gastrointestinal bleed). Both received idarucizumab.

Twenty-nine patients required urgent surgery while on dabigatran (Table 1). The most common indication for surgery was a fractured neck of femur (NOF) (six patients). Only three (10.3%) patients received idarucizumab. One each for thoracotomy for oesophageal perforation, vascular catheter insertion for acute dialysis and for an emergency tracheostomy in conjunction with open reduction/internal fixation of a mandible fracture. No bleeding complications were reported for these procedures. One (3%) patient died within 30 days of surgery (insertion of intramedullary nail for fractured femur) of their underlying medical conditions (severe aortic stenosis, severe chronic obstructive pulmonary disease and congestive heart failure) post-surgery. Patients on dabigatran who sustained a fractured NOF waited a mean of 4 days for operation (range 3–6 days). Half of these fractured NOF patients had dabigatran use and need for normal haemostasis prior to surgery specified on the theatre booking form as a reason for operative delay. It was unclear from notes review if there was a significant delay in other surgery types.

Eleven (14%) patients who were prescribed dabigatran had TT < 60 s (Fig. 2), two of which had normal TT (<21 s). Two of the patients with non-therapeutic TT still received idarucizumab for bleeding. Overall, 14 patients received idarucizumab, all of which had an indication meeting the local guideline. Only one patient did not have a TT prior to idarucizumab, the reason for this was unclear. A follow-up TT was processed in only five patients (range 4–72 h post-idarucizumab), four were within the normal range. The one abnormal sample was contaminated by heparin from dialysis. All five patients had a pre-idarucizumab TT of ≥60 s demonstrating complete and effective reversal. All TT and those with pre- and post-idarucizumab TT are shown in Figure 2. There were no documented clinical concerns of ongoing bleeding in patients who had received idarucizumab. The combination of these parameters confirms effective reversal. No thrombotic events or other adverse events were reported that were related to idarucizumab use.

Anticoagulation was restarted in 31 (60%) patients after bleeding, the mean being 21 days after bleed (range 0–270 days). Only one was switched to warfarin, and

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
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</thead>
<tbody>
<tr>
<td><strong>Bleeding group</strong></td>
</tr>
<tr>
<td>(n = 51)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td><strong>Male sex, no. (%)</strong></td>
</tr>
<tr>
<td>28 (54.9)</td>
</tr>
<tr>
<td><strong>Ethnicity, no. (%)</strong></td>
</tr>
<tr>
<td>New Zealand European</td>
</tr>
<tr>
<td>Maori</td>
</tr>
<tr>
<td>Other Europeans</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td><strong>Creatinine clearance, no. (%)</strong></td>
</tr>
<tr>
<td>≥80 mL/min</td>
</tr>
<tr>
<td>50 to &lt;80 mL/min</td>
</tr>
<tr>
<td>30 to &lt;50 mL/min</td>
</tr>
<tr>
<td>&lt;30 mL/min</td>
</tr>
<tr>
<td><strong>Indication for dabigatran, no. (%)</strong></td>
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<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td><strong>Type of surgery, no. (%)</strong></td>
</tr>
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</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Ulcer debridement</td>
</tr>
<tr>
<td>Permanent pacemaker insertion</td>
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<tr>
<td>Embolectomy</td>
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<tr>
<td>Others</td>
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<tr>
<td><strong>Bleeding characteristics, no. (%)</strong></td>
</tr>
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<td>Major</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Intracranial</td>
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<tr>
<td>Others</td>
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<tr>
<td>Minor</td>
</tr>
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<td>Gastrointestinal</td>
</tr>
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<td>Epistaxis</td>
</tr>
<tr>
<td>Haemoptysis</td>
</tr>
<tr>
<td>Intracranial</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Idarucizumab given, no. (%)</td>
</tr>
<tr>
<td>11 (21.6)</td>
</tr>
<tr>
<td>30-day mortality, no. (%)</td>
</tr>
<tr>
<td>2 (3.9)</td>
</tr>
</tbody>
</table>
the remaining 30 all restarted dabigatran. In the surgery group, 25 (86%) patients restarted anticoagulation the mean being 6 days after surgery (range 0–27 days). Of those who restarted anticoagulation, only two patients were switched to warfarin.

Discussion

This retrospective audit examined the management of patients on dabigatran presenting with bleeding or requiring urgent surgery and use of idarucizumab reversal according to local guideline. Idarucizumab was effective at reversing dabigatran when assessed by clinical and laboratory criteria. It was underutilised overall, particularly in the setting of patients requiring urgent surgery and overused in the proportion (14%) that had a non-therapeutic TT (<60 s).

New Zealand is a unique population, in that dabigatran was the only NOAC routinely available for general prescription at the time of the audit. This audit represents an unselected population with a broad age range and ethnic mix typical for a New Zealand population and also included patients with renal impairment on doses of dabigatran higher than recommended by local guidelines. This audit therefore strengthens evidence for the safe and effective use of idarucizumab, and the results are generalisable to similar populations.

We found that only a small proportion of patients requiring urgent surgery (10.3%) received idarucizumab. This does raise the concern that acute surgery may have been inappropriately delayed where the patient could have benefited from reversal with idarucizumab and earlier surgery. National and international guidelines recommend that surgery for fractured NOF should be done on the day of, or the day after, admission, and this has a statistically and clinically significant reduction in mortality and morbidity.5,10 No patient on dabigatran in this audit who sustained a NOF fracture received surgery within the recommended timeframe, and in half the cases, dabigatran was specified as the reason for delay. This suggests a role for increased use of idarucizumab to facilitate early surgery. Other patients undergoing urgent surgery likely would have benefitted from idarucizumab, but this is less clearly mandated by evidence or guideline. Lack of awareness of the availability, cost and lack of evidence supporting mortality benefit of idarucizumab may have been factors contributing to its low utilisation rate. There may be a need for increased education on the availability of idarucizumab. Although beyond the scope of this review, use of idarucizumab to facilitate earlier surgery (reducing inpatient bed-days) likely has an additional cost benefit.

The local guideline for idarucizumab was followed in most cases. Approximately, one-third of patients who received idarucizumab only had a follow-up TT. This is suggested but not mandated. Studies have shown a small number of patients’ experience rebound in TT, particularly in obese patients or patients with dabigatran overdose and high serum levels.8,11 The clinical significance of this is uncertain, but if there is concern of ongoing bleeding and TT remains elevated, a repeat dose and/or haemodialysis can be considered.12,13 Where TT were completed, effective reversal was demonstrated by both laboratory and clinical parameters.

Fourteen percent of patients on dabigatran presenting with bleeding or need for urgent surgery had non-therapeutic TT at presentation (TT <60 s). Previously, the reported rate was 20%.6,8 In previous trials, these patients were treated with idarucizumab as dabigatran could still be contributing to bleeding.8 During this audit, we had two patients with non-therapeutic TT who were managed with the same approach with no adverse events. This practice could be questioned, and we suggest that these patients do not require it, which would come at a significant cost saving to the hospital. More recent guidance from Tran et al.14 also suggests that this is a reasonable approach especially if the activated partial thromboplastin time (aPTT) is normal.

In patients presenting with bleeding, 60% resumed anticoagulation and did so with a mean of 21 days after the event. Reinstitution of anticoagulation after intracranial or gastrointestinal haemorrhage is associated with a lower risk of adverse events suggesting more patients could benefit from reintroduction of anticoagulation.12,13 Evidence suggests restarting anticoagulation between 7 and 30 days after gastrointestinal bleed is optimal in terms of balancing risks of bleeding and embolic stroke.15 Post-surgery a rate of 86% also indicates more could benefit. This audit did not examine reasons for not restarting anticoagulation. These rates are lower than in the RE-VERSE AD trial where the rates were 72.5% for the bleeding group and 90.1% in the surgery group although the rates remaining on dabigatran were higher.8 This is likely due to the availability of other agents in other countries which were not in New Zealand.

Idarucizumab was used safely and effectively in the Wellington region during the first 6 months after listing on the pharmaceutical schedule. It was likely underutilised particularly for those patients with a fractured NOF. A significant proportion (14%) of those given the medication may not have required it. Increased education should be completed to promote appropriate testing and interpretation of TT pre- and post-idarucizumab.
References
Results of a survey of cancer patients’ willingness to travel to participate in a clinical trial

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Key words
clinical trial, discrete choice experiment, neoplasm, travel.

Abstract
Only 2–3% of cancer patients enrol in a trial. We surveyed patients’ willingness to change clinician or treating centre, or to travel, to participate in trials, to improve trial recruitment. Of 188 respondents, 79% were willing to participate in a trial in at least one scenario. Increasing travel time, change in oncologist, private health insurance and out of pocket expenses decreased likelihood of joining a trial. Rural and regional patients, and those from lower socio-economic areas, were more willing to travel. To optimise access to trials, clinicians should refer within and between institutions.

Clinical trials results form the foundation for evidence-based medicine, upon which decisions are made about patient care.1 Despite clinical trial participation being supported by patients2 and clinicians, and being considered a key aspect of quality cancer care,3 only 2–3% of oncology patients in developed nations enrol in a clinical trial.4

Patient, clinician or system factors all contribute to low trial enrolment. Patient barriers include randomisation, fear of receiving a placebo, fear of side effects and additional time commitment.2,5 Clinicians may not offer clinical trials to patients due to lack of equipoise, concern about patient performance status, extra staff time, and lack of awareness of appropriate trials.4 Sponsors limit site numbers due to cost and logistic constraints.6 Clinical trials have become increasingly complex, with larger numbers of sites required for smaller numbers of patients, increasing the cost of these already expensive undertakings.7

Strategies are needed to improve enrolment to clinical trials. Little is known about the relative contribution of factors that influence patients’ willingness to participate in a clinical trial. We aimed to investigate cancer patients’ willingness to travel and/or change provider to participate in a clinical trial.

This cross-sectional cohort study enrolled patients with a current or past diagnosis of cancer; attending one of five outpatient oncology clinics within a single health district; aged ≥18 years; and English speaking.

The questionnaire, either online or paper/pen, included demographics, cancer diagnosis and treatment, and prior trial participation. An introduction explained that scenarios were hypothetical, that participation would not influence clinical care, and included description of trials concepts (Appendix I). A discrete choice experiment followed, comprising 10 scenarios using varying levels from four attributes. Discrete choice experiments use unambiguous units to provide objective quantification of the magnitude of different influences on patients’ decision, reducing bias and subjectivity in responding, compared with methods such as rating scales.8

Attributes for each scenario were: type of trial, change in treating oncologist, increase in travel time and additional cost compared with usual care (Appendix I). Participants indicated whether they would join the trial described in each scenario, or receive usual care. This design allows an estimation of the trade-offs that participants would make in the listed attributes to pursue their preferred course of action. For example, a participant might be willing to travel a longer distance if their travel costs were reimbursed and they were able to participate in an open-label study in which all participants received the study intervention. The questionnaire was refined following general population testing.

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Conflict of interest: None.
Estimating a main-effects-only logistic regression model for a design of this size requires approximately 20 observations per scenario, resulting in a minimum sample size of 120 participants for the main analysis. Demographics were reported using descriptive statistics. The main hypotheses were investigated using logistic regression estimated by maximum likelihood. The dependent variable for this regression was the proportion of respondents who chose to join the trial, and predictors were the attributes of the scenario. The effects of demographic factors and disease status were investigated by refitting the same model repeatedly to data from subsets of participants, defined as follows: metropolitan, regional and rural; and socioeconomic status. All inference assumed a type 1 error rate of $P = 0.05$.

Participants provided voluntary informed consent. This study received ethics committee approval (reference 16/03/16/5.05). Registration: Australia and New Zealand Clinical Trials Registry (www.anzctr.org.au; ACTRN1261600081415).

Of 188 respondents (Table 1), 79% indicated that they would join a trial in at least one scenario, 41 chose ‘do not join’ for all 10 scenarios, and 45 chose ‘join’ for all 10 scenarios. Overall, participants chose to join the trial in 50.2% of scenarios. If oncologist and location did not change and there was no additional cost, participants would join the trial in 70% of scenarios.

As travel time increased beyond 1 h, the proportion of respondents who would consider trial participation progressively declined to below 50% (Table 2). A small but significant effect on willingness to travel favoured remaining with the current oncologist. If a change of oncologist was required for trial participation, 58% of responses were not to participate. If patients were asked to pay out of pocket expenses beyond the cost of usual care, they were less willing to participate in a clinical trial (47% of responses were to join).

Logistic regression modelling (Appendix II, Table A1) showed that participants were significantly more willing to join a trial if they did not have to change oncologist or pay additional costs (absolute increase in proportion joining of 0.27 and 0.16 respectively). As travel time increased, preference for joining a trial decreased (Appendix III, Figure A1). However, the type of trial did not alter preferences in this model.

The logistic regression model estimated willingness to travel in a manner similar to the standard ‘willingness to pay’ analyses of economic choices, using travel time as the cost to the patient. Participants were willing to travel an extra 158 min (95% confidence interval (CI) 115–195) on average to participate in a trial if their

<table>
<thead>
<tr>
<th>Variable</th>
<th>n = 188</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>59.8 (13.3)</td>
</tr>
<tr>
<td>Year cancer diagnosed, mean (SD)</td>
<td>2015 (20.3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61</td>
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<tr>
<td>Female</td>
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<tr>
<td>Highest level of education</td>
<td></td>
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<td>Year 12 or lower</td>
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<tr>
<td>University</td>
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<tr>
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<tr>
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<td>Lung</td>
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<tr>
<td>Prostate</td>
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<td>Colorectal</td>
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<tr>
<td>Stage</td>
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<td>Metastatic</td>
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<tr>
<td>Do not know</td>
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<tr>
<td>Currently being treated</td>
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<tr>
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<td>Treating centre</td>
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<td>Public 1</td>
<td>51</td>
</tr>
<tr>
<td>Public 2</td>
<td>22</td>
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<tr>
<td>Public 3</td>
<td>56</td>
</tr>
<tr>
<td>Private 1</td>
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<td>Other</td>
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</tr>
<tr>
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<td>Prior clinical trial participation</td>
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<td>No</td>
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<td>55</td>
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<tr>
<td>No</td>
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<td>3</td>
</tr>
<tr>
<td>SEIFA†</td>
<td></td>
</tr>
<tr>
<td>Least advantaged (1–3)</td>
<td>70</td>
</tr>
<tr>
<td>Intermediate (4–7)</td>
<td>97</td>
</tr>
<tr>
<td>Most advantaged (8–10)</td>
<td>14</td>
</tr>
<tr>
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<td>7</td>
</tr>
<tr>
<td>Remoteness†</td>
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</tr>
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<td>Major cities</td>
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<td>Inner regional</td>
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<td>Outer regional</td>
<td>26</td>
</tr>
<tr>
<td>NA</td>
<td>7</td>
</tr>
</tbody>
</table>

†By postcode. NA, not available; SD, standard deviation; SEIFA, Socio-Economic Indexes for Areas.
Oncologist did not change and there were no additional costs, however, if there was a change in oncologist and additional costs, participants were willing to travel for 3 (95% CI 2–46) minutes. If the oncologist changed, or if there were additional costs, then participants were willing to travel for a mean of 77 min (95% CI 60–93) and 70 min (5% CI 52–88), respectively, assuming the other factors remained stable. Whether or not there was a change in oncologist, participants were willing to travel an extra 58 min to avoid additional costs. Whether or not there was a difference in cost, patients were willing to travel for an additional 58 min to avoid a change in treating oncologist. Overall, choices about trial participation were most strongly influenced by travel time, change in oncologist and cost, and least influenced by trial design.

Education level, disease stage, current treatment or prior clinical trial involvement did not impact participation intent. In the most practically likely scenario of change in oncologist but no extra cost, rural and regional participants were willing to travel significantly longer to join a trial than those living in a city (148 vs 27 min, \(P = 0.003\)). Lower socioeconomic groups were willing to travel significantly more than higher groups to participate in a clinical trial (179 vs 43 min, \(P < 0.001\)).

### Discussion

Most patients in this sample, with a past diagnosis of cancer, were willing to consider participation in a clinical trial, in the right circumstances. Furthermore, many would change oncologist and travel to another treatment centre to do so. Those from rural areas, of lower socioeconomic status, and without private health insurance were more likely to be willing to join a trial. This study has implications on the conduct of clinical trials from the perspective of patients, clinicians and sponsors. Although it was limited to cancer patients, the concepts could be applied to other medical conditions.

Preferences typically changed in the expected direction with a change in attribute level, for example decreasing interest with increasing travel time. However, type of trial did not influence intent to join the trial or not. Based on data that trial recruitment improves with open label, non-randomised design, we hypothesised higher intended participation if participants knew what trial intervention they would receive.\(^5,12\) The lack of difference in our study may relate to: small sample size or the brief description of types of trial. Respondents (80% of whom had not participated in a trial), may not have understood the implications of different trial designs.

Regional, rural and remote cancer patients may miss out due to lack of local trials. A previous survey of rural oncology patients found that lack of information, lack of encouragement from others and financial burden were barriers to trial participation.\(^13\) However, 53% of our rural and regional study population indicated willingness to travel 4 h. Patients should be told about available trials along with early discussion of travel commitments. They can then decline the offer if travel is prohibitive, before they become too enthusiastic.\(^14\)

For trial referral to be considered, clinicians and patients must know what trials are available.\(^15\) Registries such as the Australia and New Zealand Clinical Trial Registry and clinicaltrials.gov list open trials, but may not be sufficiently user-friendly for use during a busy clinic. ClinicTrialRefer is an Australian website and mobile phone trial identification application, allowing patients to be considered for trials within, or beyond their treating institution. Strategies are required to equip patients with the knowledge and motivation to seek out clinical trials for themselves.\(^15\) These strategies are especially relevant to rural, non-white, lower socio-economic status or less educated patients, who are less likely to participate in trials.\(^16–18\)

This study used travel time as a trade-off against perceived benefits of trial participation. Respondents’ willingness to travel for an extra hour to remain with their usual oncologist indicates the value placed on continuity of care. Many oncologists practise at different locations, and may wish to transfer a patient to a location where a trial is open, while remaining as the treating oncologist.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Level</th>
<th>Proportion who would join trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncologist</td>
<td>Change oncologist</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Do not change oncologist</td>
<td>0.58</td>
</tr>
<tr>
<td>Cost</td>
<td>Additional cost</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>No additional cost</td>
<td>0.53</td>
</tr>
<tr>
<td>Trial type</td>
<td>Randomised placebo controlled</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>Randomised open label</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Single arm</td>
<td>0.53</td>
</tr>
<tr>
<td>Travel</td>
<td>Do not travel</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>Travel half an hour</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>Travel 1 h</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>Travel 2 h</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>Travel 4 h</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Trial participants should not be expected to bear additional costs when taking part in a trial, either directly or indirectly.19 Indirect costs such as travel, meals and accommodation are barriers that are not usually budgeted for.20 Reimbursement may prevent inequitable trial access for patients who are willing to travel.16

These results have limitations. Intent after reading a hypothetical scenario may not equate to actual participation. To make the scenarios broadly applicable, they included minimal details about the hypothetical trial. Participants’ high average level of education may bias towards greater interest in trial participation. Seventeen percent of respondents reported prior participation in a trial, which is higher than the population average, but we did not ask about the type of trial.

Treating clinicians should consider giving patients the option of referral within and between institutions to facilitate trial participation. These patients indicated willingness to travel to participate in clinical trials, but beyond 1 h of extra travel, interest declines substantially. Trial sponsors should consider this when selecting trial sites, so that recruitment can be available to a broad and representative population, and recruitment can be completed in a timely fashion.

Acknowledgements

The authors acknowledge the contribution of patients and their families for taking the time to consider and respond, and site staff for distributing the survey.

References

## Appendix I

File name: Sample Scenario – version 1.2 dated 15-3-2016.docx
Title: Survey text
Description: The master document from which the survey scenarios were derived.

## Appendix II

### Table A1 Logistic regression model by attribute including the five main effects

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Estimate</th>
<th>Standardised coefficient</th>
<th>Standard error</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change in oncologist</td>
<td>0.268</td>
<td>4.405</td>
<td>0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No additional cost</td>
<td>0.162</td>
<td>2.768</td>
<td>0.06</td>
<td>0.006</td>
</tr>
<tr>
<td>Additional travel (per minute)</td>
<td>−0.002</td>
<td>−6.543</td>
<td>0.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Open label trial</td>
<td>0.091</td>
<td>1.281</td>
<td>0.07</td>
<td>0.20</td>
</tr>
<tr>
<td>Single arm trial</td>
<td>0.155</td>
<td>2.148</td>
<td>0.07</td>
<td>0.03</td>
</tr>
</tbody>
</table>

## Appendix III

### Figure A1 Proportion joining trial based on travel time (x axis in minutes), change in oncologist (top vs bottom), additional cost (black=cost, red=no cost). Green line indicates 50% likelihood of joining trial.
Acute kidney injury in acute Q fever

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Key words
acute Q fever, Coxiella burnetii, glomerulonephritis, acute kidney injury.

Abstract
Coxiella burnetii infection is not known to involve directly the kidneys. Kidney injury associated with Q fever usually manifests in the setting of chronic infection or endocarditis with development of immune complex deposition. Acute kidney injury (AKI) in the context of acute Q fever infection may be more pathologically heterogeneous. We describe two cases of severe AKI secondary to acute Q fever infection, each with marked differences in pathological characteristics, and clinical course.

Acute Q fever (causative agent Coxiella burnetii) is a zoonotic febrile illness that occurs globally. Individuals typically become infected by inhalation of contaminated aerosols when in contact with common animal reservoirs such as cattle, sheep or goats. Manifestations of Q fever ranges from a self-limiting febrile illness to organ-specific disease including pneumonia, hepatitis, endovascular infection, osteomyelitis and central nervous system involvement (e.g. encephalitis, meningitis). Septic shock is uncommon. The incubation period is approximately 20 days; however, this is largely dependent on the size of inoculum. Acute kidney injury (AKI) is rarely seen in acute Q fever. Renal impairment is usually seen in the setting of chronic Q fever associated with endocarditis, immune complex deposition or primary thrombotic disorders. We present two cases of renal injury secondary to acute Q fever seen at our institution, each with different clinical and pathologic features.

Case 1: A 38-year-old man presented to hospital with 10 days of fever, chills, watery diarrhoea and malaise. He did not report respiratory symptoms, rash or arthralgias. He had not recently travelled, and had no significant animal or occupational exposures. There was no significant past medical history, and he did not take regular medication. He lived independently in an urban coastal setting. On initial examination, he looked unwell and diaphoretic with a blood pressure of 80/60 mmHg and pulse rate of 120 beats/min, and was clinically volume depleted. There was right upper quadrant tenderness and mild hepatosplenomegaly with a normal cardiorespiratory examination. He had a computed tomography (CT) abdomen with contrast that showed non-specific inflammatory stranding in the right upper quadrant; the chest X-ray was normal. Initial bloods revealed haemoglobin 129 g/L (normal 130–180 g/L), platelets 36 × 10^9/L (150–400), white blood cell count 5.3 × 10^9/L (4–11) (lymphocytes 0.75 × 10^9/L (1–4)), sodium 124 mmol/L (135–145), creatinine 143 μmol/L (61–115), albumin 27 g/L (35–55), ALP 120 IU/L (336–92), GGT 79 IU/L (0–30), ALT 168 IU/L (0–35), AST 284 IU/L (0–35) and bilirubin 28 μmol/L (5.1–20.5). Urine microscopy revealed no evidence of microscopic haematuria. He received intravenous (i.v.) rehydration and commenced empiric i.v. ceftriaxone 1 g, vancomycin 750 mg and doxycycline 100 mg, all twice daily. Blood cultures, human immunodeficiency virus, Rickettsia rickettsii, Brucella sp. and Leptospira sp. serology were all negative. Serum creatinine initially improved markedly to 77 μmol/L on day four of admission. Initial C. burnetii serology revealed reactive Q fever Phase 2 IgM and non-reactive IgG by enzyme immunoassay (EIA), and a Q fever Phase 2 IgM of 320 on immuno fluorescence (IF). At this point, both ceftriaxone and vancomycin were ceased and doxycycline was continued for a total of 750 mg and doxycycline 100 mg, all twice daily. Blood cultures, human immunodeficiency virus, Rickettsia rickettsii, Brucella sp. and Leptospira sp. serology were all negative. Serum creatinine initially improved markedly to 77 μmol/L on day four of admission. Initial C. burnetii serology revealed reactive Q fever Phase 2 IgM and non-reactive IgG by enzyme immunoassay (EIA), and a Q fever Phase 2 IgM of 320 on immunofluorescence (IF). At this point, both ceftriaxone and vancomycin were ceased and doxycycline was continued for a total of 10 days. From day 4 to day 9 of admission, his serum creatinine rose from 77 to 562 μmol/L and the urine protein : creatinine ratio was 1300 g/mol (<100) (Fig. 1). Urine microscopy demonstrated microscopic haematuria with greater than 500 × 10^4/L red blood cells (<10). Streptococcal serology, cryoglobulins and anti-neutrophil cytoplasmic antibody testing was unremarkable. A renal biopsy was performed which showed a diffuse...
membranoproliferative glomerulonephritis with acute tubular injury and interstitial inflammation (Fig. 2). Immunofluorescence showed strong granular reactivity in the mesangium and capillary loops for IgG, C3 and C1q. There was strong granular reactivity for lambda with moderate reactivity for kappa. Electron microscopy demonstrated extensive deposits in mesangial, subendothelial and subepithelial locations. The deposits were composed of randomly arranged, structural and non-branching fibrils with a diameter between 12 and 19 nm. There was no light chain restriction or evidence of amyloidosis.

C. burnetii polymerase chain reaction (PCR) was negative on the biopsy specimen. Convalescent Q fever serology 7 days after the initial testing showed reactive Q fever Phase 2 IgM and IgG by EIA, and a Q fever Phase 2 IgM and IgG of >1280 on IF. He had a transthoracic echocardiogram that showed a left ventricular ejection fraction of 62% with no evidence of infective endocarditis. His serum creatinine reduced to 389 μmol/L, and he was discharged however represented 5 days later with fevers, night sweats and ankle swelling. His creatinine had risen to 415 μmol/L, potassium 5.9 mmol/L and bicarbonate 19 mmol/L. He was commenced on a low potassium diet and sodium bicarbonate 1680 mg twice daily and prednisolone 50 mg daily for post-infectious glomerulonephritis. His repeat urine protein:creatinine ratio had reduced to 25 g/mol and serum creatinine to 247 μmol/L 8 weeks after commencing prednisolone which was being tapered.

Case 2: A 54-year-old man presented to hospital with 1 week of epigastric pain, fever, jaundice and vomiting. He lived on a small acreage without cattle or other farm animals and worked as a truck driver. His past medical history was significant for peripheral vascular disease and tobacco smoking. On examination, he had a blood pressure of 72/40 mmHg, pulse rate 120 and temperature of 38.9°C. He had scleral icterus and large tender hepatomegaly. He was promptly transferred to the intensive care unit (ICU) with inotropic support on i.v. piperacillin/tazobactam 4.5 g twice daily. His bloods revealed sodium 124 mmol/L, bicarbonate 18 mmol/L, creatinine 534 μmol/L, bilirubin 410 μmol/L, ALP 185 IU/L, ALT 156 IU/L, AST 201 IU/L, haemoglobin 130 g/L and platelets 31 × 10^9/L. He had a CT abdomen showing hepatic enlargement with pericholecystic stranding. His antibiotics were changed to ceftriaxone 1 g and metronidazole 500 mg twice daily early on admission to ICU to treat suspected intra-abdominal sepsis and/or leptospirosis. He developed progressive kidney and liver injury with oliguria and bilirubin rising to 750 μmol/L, albumin <15 g/L and international normalised ratio 1.5 with grade 1 encephalopathy. This prompted commencement of continuous renal replacement therapy (CRRT). R. rickettsii, Leptospira sp., hepatitis A, B and E serology were all negative; serum Leptospira and hepatitis E virus PCR were also negative. Doxycycline 100 mg twice daily was added, and metronidazole was ceased. C. burnetii serology revealed reactive Q fever Phase 2 IgM and IgG by EIA, and a Q fever Phase 2 IgM of >1280 on IF. Urine protein:creatinine ratio was 281 g/mol, and a transthoracic echocardiogram did not reveal evidence of infective endocarditis. He required CRRT for 18 days and was transitioned to intermittent haemodialysis three times weekly and was commenced on i.v. epoetin alfa 5000 units three times weekly for persistent normocytic anaemia. Doxycycline was continued for a total of 2 weeks. His renal function subsequently improved, dialysis was discontinued approximately 5 weeks after its commencement and his serum creatinine reduced to 103 μmol/L.
Discussion

*Coxiella burnetii* is a pleomorphic Gram-negative cocco-bacillus with similar morphological features to *Rickettsia* species. After inhalation of infective aerosols, microorganisms proliferate in the lung and then disseminate to the bloodstream resulting in systemic disease. Severity of infection largely depends on the strain (*QPH* plasmid associated with greater virulence) and dose of microorganism inhaled. Organ-specific disease does not appear to be related to specific strains and is dependent mainly on host immune factors. Risk factors for chronic Q fever with cardiovascular system involvement include malignancy, valvular heart disease, arterial aneurysms and pregnancy. Glomerulonephritis is not typically a manifestation of acute Q fever, although it has been described previously in an Australian abattoir worker who had a renal biopsy showing no subepithelial deposits and absence of C3, C4 and C1q on IF staining. The patient responded well to doxycycline and did not require haemodialysis or corticosteroid therapy. Glomerulonephritis is more commonly a complication of chronic *C. burnetii* infection. One reported case described a patient with year-long progressive renal insufficiency who had mesangioproliferative glomerulonephritis on biopsy. Renal function subsequently improved on doxycycline therapy. Another report documents a patient who developed glomerulonephritis with C3 and IgM immune deposits in the mesangium, as well as an isolated granuloma, on a renal biopsy in the context of Q fever endocarditis. A case of thrombotic thrombocytopenic purpura precipitated by acute Q fever infection complicated by significant renal injury as a part of the thrombotic syndrome has been documented. Development of other autoimmune phenomena including anti-phospholipid antibodies in association with glomerulonephritis is also described. Autoimmune haemolytic anaemia with tubulointerstitial nephritis has occurred in a patient with acute Q fever who ultimately required a period of haemodialysis.

Case 1 developed a severe AKI with non-nephrotic range proteinuria with diffuse proliferative fibrillary glomerulonephritis shown on renal biopsy (Fig. 2). When glomerulonephritis is seen in the setting of Q fever, kidney biopsies demonstrating immune deposits are prominent but fibrils and fibrillary glomerulonephritis has not been previously described. A negative *C. burnetii* PCR on renal biopsy does not exclude Q fever as a cause of glomerulonephritis – *C. burnetii* PCR negativity on renal biopsy has been documented in chronic Q fever cases with glomerulonephritis in the past. The role of prednisolone in this setting is unclear. Interestingly, Case 1 had no strong zoonotic exposure history, nor hepatitis or pneumonia on presentation which would be typical of acute Q fever infection. The patient also developed a monoclonal hypergammaglobulinaemia that has previously been noted in chronic *C. burnetii* infection, which prompted a bone marrow biopsy; but no lymphoproliferative disorder or haematological malignancy was identified.

Case 2 had delayed initiation of doxycycline and subsequently developed septic shock and multi-organ dysfunction. Such fulminant presentations have rarely been described in immunocompetent individuals without significant comorbidities. This may indicate that a delay in appropriate antimicrobial therapy could be a risk factor for severe disease. Despite Q fever causing fulminant hepatitis and liver failure in severe cases (as demonstrated in this case), no cases requiring liver transplantation have been documented. With coexistence of septic shock and hepatic failure, differentiation between sepsis-related acute tubular necrosis and type I hepatorenal syndrome was difficult. It is possible that these two processes played a role in the aetiology of the patient’s renal dysfunction.

Case 1 developed kidney injury later in his acute presentation to hospital and did not have evidence of persistent end-organ hypoperfusion. Case 2 had evidence of fulminant liver and renal failure evident from presentation to the emergency department that was slow to resolve. This provides a clear distinction between acute haemodynamic changes in sepsis and liver failure, and delayed immunological drivers of kidney damage. The outcome of glomerulonephritis related to acute Q fever infection is largely unknown, but cases of improved renal function with appropriate antimicrobial therapy have been noted. *Coxiella burnetii* infection is an uncommon cause of community-acquired febrile illness. AKI can be an early complication of Q fever and may be incurred by a variety of mechanisms, including immune-mediated glomerulonephritis and hypoperfusion. It remains unknown whether early antibiotic therapy or corticosteroids has any effect on renal outcomes in acute Q fever.

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PERSONAL VIEWPOINT

Evolving role of Instagram in #medicine

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Introduction

In the last decade, social media has rapidly become a part of daily life. Social media platforms are dedicated online communication channels based upon the dissemination of user-generated content, community interaction and collaboration. Social media is becoming increasingly intertwined with medicine, particularly for visually rich specialties. Instagram is a free photo- and video-sharing social media application that has been utilised extensively in visually rich fields within medicine. Herein, we discuss the advantages and disadvantages of its use in modern medicine.

Abstract

Social media has become an integral part of daily life and its use is becoming increasingly intertwined with the healthcare sector. Instagram is a free photo and video sharing social media application that has been utilised extensively in visually rich fields within medicine. Herein, we discuss the advantages and disadvantages of its use in modern medicine.

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Benefits

Patient education

Before the internet, the physician–patient relationship was largely based upon an asymmetry of medical knowledge. However, patients are no longer passive receivers of information and are taking increasingly active roles in management decision. Technologically savvy patients will consult online resources including social media platforms to obtain information about their symptoms, diagnosis or treatment. Instagram lends itself to patient education, particularly for the visual disciplines. Patients can review other cases of their disease, see before and after photos of treatments and form support groups.

Education of healthcare providers

Social media has blurred the boundaries between formal and informal teaching. It has been recognised as an innovative and inexpensive supplement to traditional education resources as it overcomes time restraints and challenges of geographical location allowing international learning and collaboration. A meta-analysis by Cheston et al. has found that using social media in medical education increased engagement and overall satisfaction levels over traditional methods. Instagram offers a readily accessible means of education, which may particularly be helpful for individuals with otherwise limited access to teaching opportunities. It may be used to share difficult, interesting or rare cases by including clinical, pathological or radiological images with the clinical history. For cases that have been diagnosed, these cases act as a ‘virtual’ grand round and this has been used by major journals such as the New England Journal of Medicine. For diagnostically challenging cases, colleagues across the world can be consulted for advice.

Patient support groups

Increasing numbers of patients are sharing their medical journey through Instagram. Using hashtags, patients can share their experiences or easily find a community of patients suffering from the same condition. This may help alleviate some of the psychological burden by normalising the condition and removing stigma by having a shared experience. Users may also have practical tips specific to a disease, which is particularly helpful for orphan diseases. For certain patients, it may be empowering to find a sense of community online and enjoyable to have the chance to talk to other people who are suffering from the same disease. Some patients may also be more inclined to seek medical review as it may appear as a more accessible and realistic option after witnessing other patients’ experiences with treatment.

Accessibility

With 1 billion active users in 2018, a majority of which are young adults and adolescents, it is easy to see why Instagram should be utilised for a health perspective. It is a pre-established means of communication that is not only easy to use but free. Physicians and health organisations can disseminate health campaigns to the millions of daily users, especially as it is now more common for people to acquire news from social media outlets.

Online presence

As we progress into a more technologically advanced world, patients are increasingly seeking out information about their treating doctors. Hosting a social media page gives doctors the power to control and manage the information that patients access. Biographic detail as well as practical information like areas of expertise, procedures and services offered, contact details and opening hours can be easily provided, particularly for physicians with minimal experience in website design. Establishment of a professional Instagram page may help build a positive online image, helping to cultivate a referral base.

Negatives

Confidentiality and consent

Confidentiality is an intrinsic tenet in the physician–patient relationship. Before any identifiable information is posted online, consent must be obtained. Currently, there is no standardised universal consent form for the use of clinical images; however, it is best practice to have written consent. Currently, there is little consensus regarding whether pictures of faces should be posted and whether identifiable features should be covered regardless of whether consent was attained. Unknowingly, clinical images can become ‘viral’ and can be impossible to delete if the patient retracts consent.

Online consultations

It is inevitable that some members of the general public will ‘direct-message’ serious medical questions to doctors who have accounts on Instagram. It is important for physicians with an online presence to avoid conducting online consultations or offer individualised medical advice. It is impossible for anyone to delete completely...
their digital footprint and any interaction made online by a medical professional must not be underestimated. A single reply to a follower’s medical question may be taken out of context and disseminated to many other individuals for which the advice is not appropriate.13

**Conflicts of interest, self-promotion and financial gain**

Instagram has been used by businesses and individuals as a marketing tool. It is obvious there are conflicting interests when elements of financial incentive and the possibility of fame come into play.13 A study investigating popular posts regarding cosmetic surgery on Instagram found that well over half of the posts were of a self-promotional nature.17 Doctors on social media are uniquely positioned to appear more trustworthy and honest than traditional businesses. Vulnerable individuals may be exploited unintentionally if doctors recommend specific brands of products or are marketing their own brand.13

**Misinformation**

Instagram like all other forms of social media is not subject to stringent peer-review, or content regulation.1 Information posted can lack accuracy as it is dependent on user-generated content.3 In a survey by Shah et al.,18 the majority of respondents believed that surgeons with social media accounts must have appropriate credentials and training before being legally allowed to advertise themselves on social media platforms. For many followers, there is an inherent expectation of trustworthiness from doctors on Instagram.13,19 Care needs to be taken when posting information based on professional opinion alone, without a rigorous evidence base.

**Professionalism and digital reputation**

One’s online identity is the result of a continuous accumulation of self-produced content which can be challenging to change.5 It is important for physicians to protect their own privacy as the pervasive nature of social media is discordant with personal and professional boundaries.5,13 It is common practice for professionals in all industries to have both a personal and professional account to prevent unwanted information from ending up online forever. In the case of an online discussion, differences in opinion should be made respectfully and statements should not attempt to degrade or belittle other medical professionals.5

**Propagation of unhealthy trends**

With the advent of Instagram and other photo-editing applications, the majority of users will find themselves filtering and editing their photos leading to altered standards of beauty.12 For some users, this can lead to body dissatisfaction, feelings of inadequacy and decreased self-esteem as they desire to look a certain way or unnecessarily compare themselves to others on Instagram.2 Social media may also be an unhealthy means of validating one’s own self-worth and attractiveness which may perpetuate negative consequences for body image.2,12 For cosmetic specialties, such as dermatology or plastic surgery, this may be causing an increase in the desire for cosmetic procedures as “filters” and other forms of photographic editing blur the lines between fantasy and reality.12 Having said this, the presence of healthcare professionals on social media can also help dispel and combat digitally circulated medical myths or unhealthy and unsafe trends like the flood of sunburn tattoos, which became popular in 2015.4,20

**Developing your own Instagram: recommendations**

For doctors, there may be benefit in creating a professional Instagram account. Recommendations for this include:

1. Posting formal qualifications in the biography to assert authority.5
2. Original content should be succinct and concise. It should be of mostly educational value and link back to appropriate formal resources.16 These can include short educational videos or procedural demonstrations.4
3. Being proactive online and making regular Instagram posts or stories.
4. Preparing a disclaimer for followers with serious medical concerns and what steps can be taken in order should they wish to seek further medical attention.13
5. Preparing a legally robust consent form for the use of clinical images and patient information before any clinical information is published online.6

**Conclusion**

For visually rich specialties within medicine, Instagram has great potential as an educational tool due to its interactive and collaborative nature. Although it is currently underutilised by medical professionals, this platform is likely to become increasingly employed within the online health sphere.
Successful treatment with ponatinib for central nervous system relapse of Philadelphia chromosome-positive B-cell acute lymphoblastic leukaemia

An 82-year-old woman presented to our hospital with a 2-day history of vision impairment. She had been diagnosed with Philadelphia chromosome-positive B-cell acute lymphoblastic leukaemia (Ph + ALL). The induction treatment of imatinib (400 mg daily) and prednisolone (20 mg daily) without cytotoxic chemotherapy was started due to her age and cardiovascular comorbidities. Because of severe intolerance to imatinib, dasatinib was reduced to 40 mg/day. She sustained a complete molecular response with continuous dasatinib treatment for 7 years. On an examination at her arrival, left optic disk swelling and retinal haemorrhaging were identified. A decline in her cognitive function was also observed. Head contrast computed tomography (CT) showed an enhancing effect of the brain surface (Fig. 1A). Her cerebrospinal fluid (CSF) cell count was significantly elevated (2461/μL), and cytology showed large numbers of leukaemic cells in her CSF. Her bone marrow aspirate also showed 17% blast cells. Ph chromosome was also detected by a chromosome analysis of her bone marrow. Reverse transcription quantitative polymerase chain reaction (RT-qPCR) of bone marrow and CSF revealed the e1a2 BCR-ABL transcripts (2.8 × 10^5 copies/μg RNA and 2.4 × 10^5 copies/μg RNA respectively). Based on

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these findings, central nervous system (CNS) and systemic relapse of Ph + ALL was diagnosed. No BCR-ABL kinase domain mutations were detected by a mutation analysis. Because her leukaemic cells were resistant to dasatinib, 20 mg of intravenous dexamethasone was given for 7 days and then tapered. At the same time, she was started on ponatinib at 15 mg/day and intrathecal injection of methotrexate (15 mg weekly for 10 times). After that, no other intrathecal injections were performed. Her cognitive dysfunction and vision impairment dramatically improved within 1 week. Three weeks later, head contrast CT revealed a significant reduction in the contrast effect of the brain surface (Fig. 1B). Two months after the start of ponatinib therapy, a chromosome analysis of her bone marrow showed a normal karyotype, and the CSF cell count returned to the normal level. In addition, bone marrow RT-qPCR showed no detection of the e1a2 BCR-ABL transcripts (<50 copies/μg RNA). These results indicated that she had achieved a complete molecular response by ponatinib treatment. At the time of writing, she tolerates ponatinib monotherapy well after 13 months without any signs of relapse.

Ph + ALL is an aggressive form of adult ALL, and patients with its relapse in the CNS have a poor prognosis. Ponatinib has been confirmed to have potent efficacy in case of relapsed Ph + ALL. However, the efficacy of ponatinib for the CNS relapse in patients with Ph + ALL who have failed treatment with other TKI has not been established, and only limited data are available. It has been reported that dasatinib crosses the blood–brain barrier (BBB) and is an efficient therapy for CNS Ph + leukaemia. However, there are limited data on whether or not ponatinib crosses the BBB as well. Abid et al. presented a case report concerning the efficacy of ponatinib for treating the CNS relapse of Ph + B-ALL. They speculated that ponatinib does not penetrate the BBB because the CNS relapse occurred while taking ponatinib, and intrathecal chemotherapy is needed for the management of the CNS relapse of Ph + ALL. However, based on the fact that they did not evaluate the concentration of ponatinib in the CSF, it is difficult to conclude that the clearance of the blasts from the CNS is simply due to intrathecal methotrexate. Although the evidence is still lacking regarding the CSF transitivity of ponatinib and its efficacy for the CNS relapse of Ph + ALL, our rare case implies ponatinib may have the potential to regulate CNS involvement considering that long-term remission was achieved even after the cessation of intrathecal treatment.

Although our ponatinib therapy is not established as standard treatment for the CNS relapse of Ph + ALL, our case demonstrated the potential utility of ponatinib for managing the CNS relapse of Ph + ALL in which treatment with other TKI failed. Further studies are therefore necessary to verify the efficacy and safety of this treatment.

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Written informed consent was obtained from the patient for publication.
Bevacizumab prescribing practices for epithelial ovarian cancer in Australia

Ovarian cancer represents a source of significant morbidity and mortality in developed countries. In 2018, it was the eighth most common cancer in females worldwide. While the age-specific incidence has decreased, the absolute number of diagnoses has increased. In 2012, in Australia, there were 1384 new cases of ovarian cancer; in 2014 it was 1395. The projected number of new cases for 2017 was 1580. Most women have the International Federation of Gynaecology and Obstetrics Stage III or IV disease at diagnosis, for whom the standard treatment involves debulking surgery and adjuvant or neoadjuvant chemotherapy.

Bevacizumab was approved for first-line treatment in combination with chemotherapy, for sub-optimally debulked Stage IIIB, IIIC or Stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer by the Pharmaceutical Benefits Advisory Committee in November 2013. This approval was based on a progression-free survival benefit of 2–4 months in two phase III trials.

When publicly available Pharmaceutical Benefits Scheme (PBS) data sets were examined, an interesting trend was observed in prescription since approval. Dispensations for initial prescription of bevacizumab increased from 2169 in the first full year of prescribing (2015) to 2604 in 2017. The apparent increase in prescriptions for this indication was observed despite minimal changes in the incidence of ovarian cancer. Moreover, the absolute number of debulking procedures has not increased between 2013 (708) and 2017 (597). Assuming each patient received all six dispensations possible per prescription, this means that 362 women received bevacizumab in 2015, versus 434 in 2017, despite unchanged incidence rates, and ostensibly unchanged debulking rates.

We therefore planned to explore the potential reasons behind such a disparity from a prescriber perspective.

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An electronic questionnaire was distributed to members of the Australian and New Zealand Gynaecologic Oncology Group (ANZGOG).

There were 16 responses from 107 possible recipients. Respondents included medical oncologists (8), gynaecological oncologists (6) and other physicians (1).

Results are detailed in Figure 1. The strongest points of agreement related to the impact of change in definition of optimal debulking, and influence of multidisciplinary discussion on impression of debulking status. Respondents generally felt that there has been a change in prescribing practices over time.

The low response rate limits any strong assertions; however, our results suggest the apparent increase in bevacizumab prescribing in Australia may be multifactorial. Few physicians felt that this was due to prescribing outside PBS indications. It is possible that the actual prevalence of women who are eligible for the PBS approved indication may be more than those derived from annual rates of new diagnosis. A detailed audit of individual cases through collaboration between gynaecological oncological centres may provide greater insight into the evolving changes in bevacizumab prescribing.

Across all indications, bevacizumab is the 27th most costly drug to the PBS; an average dose costs $2249. Given that updated results of ICON 7 revealed a modest overall survival benefit in subgroup analysis only, and failed to demonstrate an overall survival benefit at all in Gynecologic Oncology Group (GOG) 218, judicious prescribing of such therapy is recommended.

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References


Chronic hepatitis E infection in an immunosuppressed, solid organ transplant patient

A 48-year-old Australian-born man with a history of double lung transplant for cystic fibrosis-related lung disease in 1994, and renal transplant for calcineurin inhibitor-related toxicity in 2001, presented with a 12-month history of elevated gamma-glutamyl transferase (GGT), to approximately 300 U/L. Medications included tacrolimus, mycophenolate mofetil, prednisone,
lantus, omeprazole, cholecalciferol and trimethoprim/sulfamethoxazole.

Viral hepatitis (hepatitis A, B, C, CMV, EBV, HSV) and autoantibody testing were unremarkable. Ultrasound showed normal biliary tree and no evidence of cirrhosis. Liver biopsy demonstrated chronic hepatitis, interface and lobular changes with lymphocytic and eosinophilic infiltrate, and mild peri-portal fibrosis, thought consistent with a drug reaction. Trimethoprim/sulfamethoxazole was ceased. Magnetic resonance cholangiopancreatography showed filling defects in the common bile duct. Three stones were removed at endoscopic retrograde cholangiopancreatography (ERCP).

Six weeks after ERCP, he developed jaundice (bilirubin 500 umol/L). GGT had declined; but alanine aminotransferase had risen to approximately 300 U/L, indicative of a new pathology. This occurred approximately 6 months after travel to England and France. He developed ascites and grade 2 hepatic encephalopathy. Hepatitis E virus (HEV) serology and polymerase chain reaction for HEV RNA in serum and stool were positive. Testing of stored serum from 6 months prior to onset of jaundice for HEV serology and RNA was also positive. Genotyping revealed genotype 3 HEV. Repeat liver biopsy showed chronic HEV with marked progression in fibrosis.

He was treated with ribavirin and reduction in immunosuppression (tacrolimus dose reduced, aiming levels 4–6). Unfortunately, he developed sepsis with decline in renal function. Liver transplantation was considered but he was too unwell to proceed, and there were concerns regarding persistent HEV infection post-transplant. He received palliative care and died.

Acute HEV is rare in Australia,1 and is usually only seen in patients with recent travel. The incubation period is between 2 and 10 weeks.2 HEV can cause chronic infection in immunosuppressed patients.2 Chronic HEV is defined as the presence of HEV RNA in serum or stool for at least 6 months.2 HEV genotypes 1 through 4 exist; however, chronic infection has only been described with genotype 3.3 HEV is endemic in southwest France, and is transmitted by consumption of infected pork, offal, mussels and fruit and vegetables irrigated with contaminated water.3 Swine HEV infection appears to be prevalent in Australian commercial piggeries.1

A retrospective study of 85 adult solid organ transplant recipients with evidence of HEV found 65.9% developed chronic infection,4 with 9.4% of these patients developing cirrhosis.4 Liver fibrosis can evolve rapidly in solid organ transplant recipients, leading to hepatic decompensation and death.3

Ideally, candidates for liver transplantation with chronic HEV should clear the virus prior to transplantation as infection may recur and lead to cirrhosis in the graft.3 Reducing immunosuppression can clear HEV in around one-third of patients.3,4 Small series have evaluated ribavirin monotherapy and found that sustained virologic response is achieved in approximately 80% with a 3-month course.2

This case demonstrates that chronic HEV can occur in immunosuppressed patients in Australia, and should be included in the differential of immunosuppressed patients presenting with unexplained hepatitis.

References


General correspondence

Proton-pump inhibitor overuse: a cautionary tale in misguided benefit

We congratulate Leitinger et al.1 and co-authors for their comprehensive review on the use of proton-pump inhibitors (PPI) in patients with malignant haematological conditions. The authors highlight the high prophylactic and often extended use of PPI in patients receiving treatment for multiple myeloma, lymphoma and recipients of autologous haemopoietic stem cell transplantation. In those with multiple myeloma or lymphoma there was no strong indication for the initiation of PPI in more than half the patients studied. Furthermore, therapy was typically continued for a protracted duration, sometimes indefinitely despite no indication for therapy. Studies involving the general population from the United States and the United Kingdom have also reported up to 70% of PPI prescription without indication.2,3 The authors have also highlighted the paucity of robust evidence on the indications for prophylaxis in those patients receiving glucocorticoid therapy. Their national survey demonstrated high variability in clinical practice and an overall lack of institutional protocols for the use of PPI therapy in this setting.

PPI therapy has been widely regarded as safe and well tolerated, and it seems this belief perpetuates its use beyond the desired indication. The work by Leitinger et al.1 increases the awareness of the potential toxicities of PPI therapy. However, an important and increasingly recognised association of kidney disease in the setting of PPI overuse needs to be highlighted. Several large multinational observational studies have consistently demonstrated an association between PPI use and development of chronic kidney disease (CKD), progression of CKD and development of end-stage kidney disease, even without intervening acute kidney injury.3,4 Studies have also suggested a graded relationship between kidney injury and duration of drug exposure.4 However, the mechanism of injury remains to be elucidated, but appears to be driven by an interstitial pathology rather than glomerular disease itself.4 These findings reiterate the importance of judicious use of PPI in an already vulnerable patient population who remain at risk of kidney disease from the malignancy and chemotherapy itself.5 With an ever-increasing repertoire of novel cancer therapies demonstrating improved survival outcomes, there needs to be a greater focus on survivorship and long-term treatment toxicities.

We fully support Leitinger et al.1 in their call for increased pharmacovigilance when prescribing PPI, not only in patients being treated for haematological malignancies, but also other medical patients as well. These concerns should not deter clinicians from prescribing PPI when indicated, but should reinforce the need for a measured approach in prescription and de-escalation.

In contrast to disease-modifying treatments, supportive care in malignant haematology is often not reinforced by a strong evidence-based approach. We hope that studies such as this, encourage institutions and national bodies to develop robust, evidence-based guidelines on the safe prescription of supportive therapies in cancer.

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References
Maintaining a fit T-cell compartment: lymphoma treatment sequencing in the era of chimeric antigen receptor T-cell therapies

We welcome the recent publication by Trotman et al., presenting approaches to front-line treatment of follicular lymphoma (FL) in Australia.\(^1\) Trotman et al. highlight the potential application of bendamustine combinations for FL front-line and in relapsed disease.\(^2\) In the absence of an overall survival (OS) benefit favouring a particular chemotherapy backbone, both bendamustine and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) are recommended by the authors, in combination with an anti-CD20 antibody.\(^1\) There are benefits of bendamustine in terms of lower early toxicity and longer progression-free survival, at the potential cost of increased late infection and second malignancy rates.\(^1\)\(^,\)\(^3\)\(^,\)\(^4\) We highlight an additional factor of emerging importance in treatment selection for non-Hodgkin lymphoma: the potential impact on subsequent chimeric antigen receptor (CAR) T-cell therapy.

CAR T-cell therapies directed against CD19 are licensed for relapsed and refractory aggressive B-cell lymphoma treatment internationally, including in Australia. Early phase trials indicate CD19 CAR T cells are similarly able to induce durable remissions in other B-cell lymphomas, including FL.\(^5\) If the apparent plateau of relapses seen in aggressive B-cell lymphomas holds true in larger FL trials, CAR T cells have the potential to compete with allogeneic stem cell transplantation to deliver long-term remission.

Trotman et al. note the prolonged T-cell lymphopenia associated with bendamustine use.\(^1\)\(^,\)\(^4\) Production of CAR T cells requires an adequate T-cell harvest, circulating T-lymphocyte levels <350/μL being strongly associated with CAR T-cell production failure.\(^6\) Treatments that cause prolonged T-cell lymphopenia therefore have the potential to preclude subsequent CAR T-cell therapy.

Units across Australia are already delivering CAR T-cell therapies. This includes a trial in high-risk, relapsed FL (NCT03568461). Until results of this and similar trials are available, the role of CAR T cells for FL remains uncertain. However, we believe that, as OS is similar between the front-line treatment options, avoiding T-cell depleting chemotherapy regimens should be a consideration when discussing treatment options with younger patients who are potential future CAR T-cell therapy candidates.

In summary, because chemotherapy is not curative for advanced FL, it is critical to maintain a long-term perspective of treatment options. Maintaining a ‘fit’ T-cell compartment may be an increasingly important consideration in the era of CAR T cells.

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Author reply

We thank Dickinson and Weinkove\(^3\) for their letter in response to our article on the frontline management of follicular lymphoma (FL) in Australia.\(^2\) They highlight the prolonged CD4 lymphopenia following the use of bendamustine, and theoretical potential to impede T-cell harvest for the production of chimeric antigen receptor (CAR)-T cells. We too are most encouraged by the early phase data of CD19 CAR-T cell immunotherapy in relapsed/refractory and transformed FL. In the most recent
of these studies, Hirayama et al. reported 13 of 21 (62%) patients with relapsed/refractory or transformed FL obtaining a complete response, many of which were sustained beyond 2 years.3 We are also heartened by the clinical trial access to CAR-T cells at limited sites in Australia. Nonetheless, the immaturity of data in FL, and its expense, will likely preclude widespread availability of this approach in Australia and New Zealand for some years.

Although we acknowledge that FL is incurable, the prolonged remissions seen following effective first line therapy likely provides a ‘functional cure’ for many patients (who have a median age at presentation of 60). For younger patients, with an anticipated median PFS beyond 15 years after anti-CD20 antibody-bendamustine chemotherapy, we can anticipate for most patients any CD4 lymphopenia will have resolved at the time of any relapse.4 Martínez-Calle reported a median time to lymphocyte count recovery (≥1 × 10⁹/L) following bendamustine of 26 months with rituximab maintenance associated with further delays in recovery.5 Saito observed recovery of lymphocyte and CD4-positive T-cell counts to those at baseline at 7–9 months after the completion of bendamustine.6 There is a paucity of data on the ‘fitness’ of the T-cell compartment over time and the ability to generate CAR-T cells, from bendamustine-treated patients. Whether the small risk (<10%) of early progression and/or transformation of disease within the first 2 years justifies avoiding bendamustine in the first-line treatment is unclear. We lack adequate pre-treatment prognostic factors for FL to inform fully the choice of first line therapy in a given patient. Perhaps the impact of CD4 lymphopenia following bendamustine on T-cell fitness for immunotherapy will be more relevant in subsequent lines of therapy.

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Access to linked data: challenges and progress

The paper by Palamuthusingam et al. describes the challenges faced by researchers wishing to access Australian linked data.1 We agree with several points they make. Their experience replicates the experiences of others as highlighted in several Government reports.2,3 We also agree that the Population Health Research Network’s (PHRN) role includes advocating for changes that will improve access to linked data for researchers. However, the article included out of date information and misinterpretations that should be clarified.

The PHRN is not a ‘central body’ but a national collaborative network of government agencies and academic institutions. Despite the challenges described in the article, this collaboration has significantly improved access to linked data. In 2009, two states
(WA and NSW) had data linkage units (DLU) and now all states and territories are serviced by DLU. Access to cross-jurisdictional linked data was restricted to a few special programmes or ad hoc arrangements. Today, all researchers can apply for access to cross-jurisdictional linked data through a coordinated online application process.

The authors were critical of the number of publications attributed to the use of the new DLU based on a paper by Tew et al. This paper only included publications involving linked hospital data and counted publications up to 2014 when the new DLU were still in their infancy. Many researchers receiving data through these facilities would not have had time to complete their analysis and publish their results. More recent publications data are available and could have been cited.

The legal and ethical frameworks in which data intensive research must be conducted are complicated and overlapping. The authors claim that their example only involves non-identifiable data and can be exempt from ethical review (National Statement 5.1.22). However, it could not be exempt under Section 5.1.22 because it uses existing identifiable data collections and identifiable data are used to create links between the data collections. The detailed clinical data provided to the researchers for analysis may also be identifiable (National Statement 3.1 Element 4). In addition, the waiver of consent to link the data must be approved by a human research ethics committee (National Statement 2.3.9). The authors also imply that data custodians are insisting on ethics review unnecessarily, however, HREC review may also be required to meet legal requirements under the statute governing the particular data collection.

The authors note that projects involving linked data are currently excluded from the National Mutual Acceptance Scheme (NMA) by several jurisdictions. The PHRN participated in the development of a report to the NMA Jurisdictional Working Group which made recommendations about including linked data in the NMA. The report is currently under consideration by the Working Group.

Finally, the authors are supportive of the recommendations in the Productivity Commission Report but fail to acknowledge that the Australian Government has accepted the report and are in the process of implementing the recommendations. The PHRN will continue to advocate for these and other initiatives to improve researcher access to Australian linked data.

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raised by Flack and Smith\(^2\) and take this opportunity to elaborate.

First, Flack and Smith\(^2\) refer to the coordinated online application process. However, even at the time of writing this reply, this application process is not universally accepted by several large jurisdictions who still require their own application to be completed. We would strongly welcome a centralised process to streamline applications, but unfortunately this is still not yet a reality.

Second, pertinent to our experience was the use of hospital admission datasets and hence the article by Tew et al.\(^3\) was the most relevant as this was the dataset of interest in their systematic review. Flack and Smith\(^2\) identify a more recent review by Young and Flack\(^4\) demonstrating a positive trend in research output when considering all other datasets. This is a promising finding but was published well after submission of our narrative reflection.

Finally, we do not dispute that human research ethics committee (HREC) approval is essential when undertaking data-linkage projects and we advocate that all researchers undertaking data-linkage seek ethics approval for the reasons outlined in our narrative.\(^1\) Our intention was to highlight the inconsistency between different jurisdictions’ review processes, whereby custodian consultation could only occur after HREC approval running the risk that custodians modify research requests resulting in HREC amendments that would have been avoided had the custodian consultation occurred earlier in the process. We also wished to highlight the national mutual acceptance memorandum is inconsistently applied across jurisdictions and we welcome the PHRN’s ongoing contribution to achieving national acceptance.

With an ever-increasing emphasis on data-linkage research, we support the sentiments of Flack and Smith\(^2\) that comprehensive ethical and legal frameworks are equally as important in creating effective data-linkage infrastructure. We also wish to emphasise that a unified consistent process is essential to maximise the utility of this valuable resource. The PHRN’s leadership in harmonising the currently fragmented approval process for multi-jurisdictional data-linkage is greatly appreciated and welcomed.

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Corrigendum

The Publisher would like to draw the readers’ attention to an error in the following article:


Jessica Nasseh’s name was corrected.

The authors apologise for the error.
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1 Out of 42 patients who discontinued Soliris® 21 reintiated, with 1 in 2 reintiliations due to TMA or renal impairment.⁶
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References:

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