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Stroke thrombolysis: *per ardua, ad astra* . . .

It is now approaching 20 years since the publication of the first research trials on the use of recombinant tissue plasminogen activator (tPA) in the treatment of acute ischaemic stroke.\(^1\) To date, there have been 12 randomised controlled trials in tPA stroke thrombolysis, the most recent being the International Stroke Trial (IST3).\(^2\) For various reasons, all the trials have garnered their fair share of controversy, a testament to the fact that stroke is a complex and heterogeneous disease that not infrequently defies containment within the context of traditional research methodologies. Nevertheless, our knowledge base of stroke thrombolysis continues to expand, and the totality of evidence through pooled data analysis clearly indicates that the therapeutic benefit of tPA is time-dependent, is greatest when given early after stroke onset but diminishes over the subsequent time up to 4.5 h. Indeed, when used appropriately, tPA is one of the most effective treatments for acute ischaemic stroke, with a number needed to treat ranging from 4.5 (if used within 3 h) to 14 (if used within 4.5 h).\(^3\) This benefit occurs despite an increase in the number of early symptomatic intracranial haemorrhages (sICH) and early deaths. Data from a large USA stroke registry of 58 353 tPA-treated patients were able to investigate the temporal effect of delays in tPA treatment.\(^4\) The results indicated that earlier thrombolytic treatment was associated with higher rates of independent ambulation at discharge and higher likelihood of discharge to home. Importantly, it revealed that adverse events are themselves also time dependent, with reduced occurrence of sICH and reduced mortality, and are related to earlier stroke onset to treatment time.\(^5\) Recent data from the IST3 are consistent with the direction of previous analyses. There is benefit for patients over the age of 80 years of age, and while treatment out to 6 h did not quite reach significance, there are clinically relevant (and statistically significant) improvements in functional outcome and health-related quality of life that are sustained for at least 18 months. The upcoming publication of an individual patient meta-analysis will hopefully add further clarity to this debate.\(^6\)

So, herein lies the crux of the issues that link three recent papers published in the *Internal Medicine Journal* – the need for speed in commencing stroke thrombolysis, but doing so in a safe manner to minimise any serious adverse outcomes, in particular the occurrence of symptomatic intracerebral haemorrhage. All three papers highlight different elements of the complexities of delivering stroke thrombolysis.

As noted, a fundamental component of tPA stroke thrombolysis is that time has a strong influence on the magnitude of treatment benefit. Brain imaging studies show that the volume of irreversibly injured tissue in acute ischaemic stroke expands rapidly over time; Saver *et al.* has estimated that 2 million neurons per minute are lost until vessel reperfusion is achieved.\(^4\) This emphasises the maxim that ‘time is brain’, and delays to commencing reperfusion therapy can have devastating consequences. In this context, Tai and Yan\(^6\) review strategies for minimising in-hospital and out-of-hospital delays to treatment with tPA thrombolysis. In the prehospital environment, the early recognition of stroke symptoms has been well executed through the successful FAST (Face, Arm, Speech, Time) advertising campaign (National Stroke Foundation) and has led to a significant increase in the number of people who can recall the warning signs of stroke.\(^7\) Paramedic recognition of stroke has also improved considerably through the use of specific prehospital clinical tools with high sensitivity. Alerting the receiving hospital to impending arrival (prehospital notification) is a critical next step and has been shown to increase significantly rates of stroke thrombolysis.\(^8-10\) These approaches are best implemented across healthcare services, and indeed, many Australian ambulance services have updated clinical protocols to enable a system-wide approach, with excellent results.\(^5,11\)

The paper by Nusa *et al.*\(^12\) investigates the use of a blood clotting point of care device (CoaguChek XS System; Roche Diagnostics, Mannheim, Germany) to derive quickly international normalised ratio (INR) prior to commencing stroke thrombolysis. Standard laboratory INR testing can take up to 30 min (or longer), which is unacceptable in the context of the time-critical treatment of acute ischaemic stroke. They found that there is a very good correlation between the INR derived from the point-of-care device and the laboratory INR reading. The study excluded those who were known to be taking oral anticoagulants. In standard clinical practice in the absence of any known clinical risk for an abnormal clotting profile, or history of anticoagulant use, many centres do not routinely undertake a clotting profile test prior to commencing tPA, a practice that is supported by recent guidelines.\(^13\) Added to this is that stroke thrombolysis is routinely
undertaken in patients taking warfarin as long as the INR is less than 1.7. Having established the validity of a point-of-care coagulometer in a normal population, it would therefore be useful to repeat this study in a population of patients with acute ischaemic stroke who are taking warfarin and therefore at higher bleeding risk. The recent PBS listing of novel oral anticoagulant (NOAC) therapies (e.g. the direct factor Xa inhibitors Apixaban and Rivaroxaban, and the direct thrombin inhibitor Dabigatran) adds a further dimension to this. These new agents have rapid onset and rapid reversal of their anticoagulant effects and therefore represent a new set of challenges in determining clotting profile status in patients with acute ischaemic stroke. For NOACs, the INR is a much less reliable indicator of anticoagulant efficacy, and other measures such as activated partial thromboplastin time and thrombin clotting time may be needed. These are only qualitative or semiquantitative measures of the anticoagulant effect of these medications, and as yet point-of-care devices to perform these tests are not readily available.

The risk of sICH in patients receiving warfarin (INR >1.7) is low. Data from a nationwide USA registry of 23 437 patients receiving tPA stroke thrombolysis indicated that 7.7% of patients treated with tPA stroke thrombolysis were on warfarin. The risk of sICH was about 5%, but after adjustment for baseline clinical factors (in particular age and stroke severity), there was no difference to those who were not taking warfarin. There were no differences in in-hospital mortality and no differences according to the actual degree of anticoagulation. Also of interest is that almost 50% of warfarin-treated patients who met American Stroke Association guideline criteria (i.e. INR >1.7) for stroke thrombolysis were not thrombolysed. This clearly represents an undertreated population of patients with acute ischaemic stroke.

However, it is improvements in the in-hospital processes of care that have undergone the most change of late. What used to be considered the ‘golden hour’ from arrival to treatment (‘door to needle time’ – DTNT) has now been reduced to 20 min through strategies such as prehospital notification of arrival by paramedics Code Stroke teams, and a direct to computed tomography triage process. Each member of the Code Stroke team knows their role and the clinical process that needs to be followed. This works well in-hours when resources are plentiful, but studies have shown that out-of-hours DTNT and stroke mortality do worsen – a so-called ‘weekend effect’. This is common in most hospitals, more so in rural and regional areas where specialist resources are even less available. Simply putting on more medical and nursing staff is not viable – a creative response is required and the rapid advances in telehealth may provide the solution that is needed. There are now extensive stroke telemedicine networks across Europe and North America, with published guidelines for implementation. Typically, these networks consist of a stroke centre ‘hub’ that services a number of ‘spoke’ hospitals. A stroke telemedicine service runs 24/7/365, and there are now well-published data to demonstrate that stroke thrombolysis rates and longer term outcomes in spoke hospitals are equivalent to those of the hub hospital and are significantly better than in those hospitals without a stroke telemedicine service. Stroke telemedicine is cost-effective. The need to transfer stroke patients to other hospitals is significantly reduced, an expense that consumes a large part of the budget of smaller rural and regional hospitals in Australia. Stroke telemedicine is not yet well established in Australia, but large-scale, statewide networks such as the Victorian Stroke Telemedicine programme are currently being implemented.

The final paper in this stroke thrombolysis trio is a case report of tPA thrombolysis performed in a young patient with a severely disabling stroke (NIHSS 15) because of infective endocarditis. In Brownlee et al. multi-modal CT brain imaging was undertaken and revealed evidence of early infarction with middle cerebral artery branch vessel occlusion. Despite treatment with tPA, further stroke events occur, and a magnetic resonance imaging revealed new, multifocal areas of infarction in both hemispheres. The patient became febrile, and an urgent echocardiogram revealed vegetations on the mitral valve. Again, tPA treatment is time critical, and it is not uncommon for the embolic source to declare itself some time later after treatment has been completed. So, to treat or not to treat? In this case, the diagnosis of infectious endocarditis (IE) was not immediately apparent, and treatment guidelines were clearly followed correctly. However, as the authors highlight, in the context of known IE, there is a higher risk of complications with the use of tPA. If IE was identified earlier, are there options other than tPA? Endovascular treatments are certainly a consideration but remain unproven, with recent studies (albeit in non-IE patients) indicating no benefit compared with tPA alone. But even from these negative trials, an important message comes to the forefront: there is no benefit from recanalisation if it occurs too late... so do not delay, time is brain!
References

On 5 May 2013 it was World Pulmonary Hypertension (PHT) Day. It coincided with the 30th anniversary of the first death in Spain of a child who died of pulmonary arterial hypertension (PAH) after exposure to toxic rapeseed (canola) oil. The appalling outbreak of what was then called ‘primary pulmonary hypertension’ (PPH) (almost exclusively in females) affected approximately 20% of those exposed highlighting the capriciousness of a disease requiring both genetic predisposition and environmental triggers. The subsequent substantial advances in our understanding of and approach to therapy in PHT was highlighted during the recent 5th World Symposium on Pulmonary Hypertension in Nice, France in February 2013. Although the official proceedings of the symposium will not be published until early 2014, the meeting provides an impetus for this paper reviewing the current situation and implications for the approach to PHT in Australia and New Zealand in 2013.

Definition and diagnosis

PHT is a relatively common finding, haemodynamically defined as mean pulmonary artery pressure ≥25 mmHg on right heart catheter (RHC). No definition currently exists for exercise-induced PHT not because it does not exist but because based on the present evidence, its clinical relevance is unclear. In Nice, only minor modifications were made to the classification of the more than 40 associated or direct causes of PHT (Table 1). PHT is usually first suspected at echocardiography in patients being investigated for exertional-related dyspnoea or unexplained syncope, and then must be confirmed by RHC. Only in patients with PAH (Group 1 in Table 1) with pulmonary artery occlusion pressure generally referred to as pulmonary capillary wedge pressure (PAWP) of <15 mmHg and an increased pulmonary vascular resistance >3 Wood units do we have robust evidence for use in clinical practice of targeted pulmonary vasodilator therapies. The many pitfalls in non-invasive diagnosis still mandate RHC for definitive diagnosis of PH. Indeed considerable time was devoted in Nice to the appropriate methodology of RHC. The measurement of pulmonary artery pressure in terms of prognosis and...
**Table 1** Classification for pulmonary hypertension

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pulmonary arterial hypertension (PAH)</td>
</tr>
<tr>
<td>1.1 Idiopathic (PAH)</td>
</tr>
<tr>
<td>1.2 Heritable</td>
</tr>
<tr>
<td>1.2.1 BMPR2</td>
</tr>
<tr>
<td>1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)</td>
</tr>
<tr>
<td>1.2.3 Unknown</td>
</tr>
<tr>
<td>1.3 Drugs and toxins induced</td>
</tr>
<tr>
<td>1.4 Associated with (APAH)</td>
</tr>
<tr>
<td>1.4.1 Connective tissue diseases</td>
</tr>
<tr>
<td>1.4.2 HIV infection</td>
</tr>
<tr>
<td>1.4.3 Portal hypertension</td>
</tr>
<tr>
<td>1.4.4 Congenital heart disease</td>
</tr>
<tr>
<td>1.4.5 Schistosomiasis</td>
</tr>
<tr>
<td>1.4.6 Chronic haemolytic anaemia</td>
</tr>
<tr>
<td>1.5 Persistent pulmonary hypertension the newborn</td>
</tr>
<tr>
<td>1.5 Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis</td>
</tr>
<tr>
<td>2 Pulmonary hypertension due to left heart disease</td>
</tr>
<tr>
<td>2.1 Systolic dysfunction</td>
</tr>
<tr>
<td>2.2 Diastolic dysfunction</td>
</tr>
<tr>
<td>2.3 Valvular disease</td>
</tr>
<tr>
<td>3 Pulmonary hypertension due to lung disease and/or hypoxaemia</td>
</tr>
<tr>
<td>3.1 Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>3.2 Interstitial lung disease</td>
</tr>
<tr>
<td>3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
</tr>
<tr>
<td>3.4 Sleep-disordered breathing</td>
</tr>
<tr>
<td>3.5 Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td>3.6 Chronic exposure to high altitude</td>
</tr>
<tr>
<td>3.7 Developmental abnormalities</td>
</tr>
<tr>
<td>4 Pulmonary thromboembolic pulmonary hypertensive</td>
</tr>
<tr>
<td>5 PH with unclear and/or multifactorial mechanisms</td>
</tr>
<tr>
<td>5.1 Haematological disorders: myeloproliferative disorders, splenectomy</td>
</tr>
<tr>
<td>5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis</td>
</tr>
<tr>
<td>5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders</td>
</tr>
<tr>
<td>5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis</td>
</tr>
</tbody>
</table>

PAWP is unreliable or unavailable; and the use of a fluid challenge to unmask left ventricle diastolic dysfunction as key measurements were all the focus of considerable discussion.4,5

**Epidemiology**

The term PHT is often been used interchangeably with PPH which should now be referred to as idiopathic PAH (iPAH) (World Health Organization (WHO) Group 1). This was thought to be a rare disease almost exclusively seen in young females. Widespread use in the 1970s of the appetite suppressants dexfenfluramine and fenfluramine led to substantially increased cases of PPH in regions of major use (USA and Europe). The surge in cases of PPH prompted world experts to gather for the first world symposium on PHT that was sponsored by the WHO.6 Subsequently, the (USA) National Institutes of Health (NIH) funded the first multicentre registry for PHT, estimating an incidence rate for so-called PPH of one to two cases per million within the general population.7

In Nice, there was considerable discussion as to whether the demographics of PHT were changing. The overall impression of clinicians in the field was that there are more cases, with older age at diagnosis and less female predominance.8 Potential causes for the apparent increase included: a true increase, greater ascertainment of cases (particularly of Groups 2–5 PHT; Table 1), improved survival (increasing prevalence) or a combination of these factors. Disappointingly, despite increasing evidence for an increase in patient numbers, no consensus could be reached on the true increase in prevalence rates.9–12

It was not until 2007 that the French National Registry reported an increase in both incident (2.4 cases/million) and prevalence (15 cases per million) of PAH. Within this unique French National Registry, identified for the first time, a wide variable range of regional prevalence (of PAH) had been found (ranging from 5 to 25 cases per million).10 Additional supportive data, extracted from all Scottish hospital discharge record groups based on International Classification of Disease codes confirmed the incidence and prevalence rates had risen over time to incidence rates of 7.1/million/year and also documented prevalence rates of 52 cases/million, respectively, for PAH (iPAH, PAH associated with connective tissue disease and PAH associated with congenital heart disease). Secondly, there was a large discrepancy in prevalence estimates between the Scottish Hospital data (52/million) and the so-called ‘centre of excellence’ data from the Scottish Pulmonary Vascular Unit (SPVU) (26 cases/million). The SPVU is tasked with responsibility for ‘all’ cases of PHT within Scotland, and yet, there was nearly double the reported numbers extrapolating from the ‘all hospital
data’ compared with those presenting to the SPVU (52 cases from all Scottish hospitals vs 26 cases per million at the SPVU).\textsuperscript{13} In Nice, registries from other parts of the world were discussed. French, Spanish and USA (Registry to Evaluate Early And Long-term PAH disease management (REVEAL) vs NIH) show a substantial increase in age and male gender in patient cohorts diagnosed with PAH in recent years.\textsuperscript{8} The CompEra, predominantly European-based registry, report a mean age at diagnosis of 66 years with 41% of male gender.\textsuperscript{14} The Chinese registry data show demographics (mean age 36 years predominantly female) that are more reflective of what was seen in the NIH registry data of more than 20 years ago.\textsuperscript{15} The majority of data generated to date from registries is primarily related to epidemiology focused on Group 1 PHT (Table 1).

A recent report from Australia would support the hypothesis that the higher prevalence of PHT is not due to the selection bias of tertiary centres established to handle referrals for PHT.\textsuperscript{9} This study evaluated unselected echocardiographic evidence from a single echocardiography centre in a geographically defined population. In a total of 15 633 echocardiograms of 10 314 patients (from 2003 to 2009) using an estimated pulmonary arterial pressure $>$40 mmHg to define the presence of PHT, all cause PHT was estimated to be 3260 cases per million within this population. The prevalence of PAH (confirmed after RHC) was estimated to be 150 cases per million. These may even be underestimates of prevalence, as in a third of this patient group, an estimate of pulmonary artery pressure was not obtained due to an insufficient tricuspid regurgitation velocity envelope.

Furthermore, the study identified a proportion of patients (15%) with an echocardiographically elevated PASP in whom, after review of medical records, referral data and the echocardiograph itself had not undergone any formal evaluation, nor did they have an established diagnosis to explain their PHT. It is becoming apparent that there may be an emerging pattern of under recognition of PHT within the Australian context at least (Fig. 1).

The authors also examined survival rates. The best survival is in those patients treated with specific therapy for PAH. Those with no treatment/ unidentified causality or those with WHO Group 2 (left heart disease) and WHO Group 3 (respiratory disease) did less well (Fig. 2). Notwithstanding the limitations of data derived from echocardiography, the community burden of PHT and the impact on mortality are clear.

The fact that many patients with PHT were not assessed by PHT expert centres is of concern. This is in part because PHT, even that seen most commonly complicating cardiac (WHO Group 2 – Table 1) and pulmonary disease (WHO Group 3 – Table 1), if present can be life-threatening.\textsuperscript{10} The Western Australian study, if extrapolated, would indicate $>$74 000 patients with PHT across Australia and $>$14 000 within New Zealand.\textsuperscript{9} Breathlessness is the cardinal symptom of PHT; however, it can be due to many other causes. Breathlessness may be variably reported rendering PHT difficult to diagnose clinically.\textsuperscript{3,17,18} Many ‘PHT centres’ are finding that a substantial number of patients referred for investigation of PHT found on echocardiogram have normal left ventricular systolic function but evidence of impaired diastolic relaxation.
finding of left ventricular diastolic dysfunction with or without PHT appears a common finding (particularly with increasing age); however, the presence of increased PASP has been shown to be an independent predictor of mortality even after adjusting for age and cardiopulmonary disease.\(^\text{19}\) The Western Australian data suggest clinical suspicion for the presence of PHT is low, and as a result, symptomatic patients are not sufficiently investigated. PHT is not a diagnosis, simply a haemodynamic finding that requires further investigation.

**Delay in diagnosis**

One very concerning finding in the initial NIH registry was a delay from first symptom to diagnosis of PHT of over 2 years.\(^\text{7}\) In the two decades since, the profile of PHT has increased, and three classes of specifically targeted drug therapies have become broadly available.\(^\text{20}\) Despite this, much discussion in Nice focused on the common view that diagnosis was still unacceptably delayed in PHT generally and in Group 1 PAH patients particularly. Two European studies and one recent from the United States of America have confirmed the current delay to diagnosis within this population.\(^\text{10,21,22}\) The French National Registry commented on the delay to diagnosis within the French population, reporting a 2.25-year delay from symptom onset to diagnosis in those patients diagnosed from October 2002 to October 2003.\(^\text{10}\) In the US REVEAL registry, the average delay in diagnosis reported within the diagnostic years of 2006 and 2007 was 35 months (or 2.9 years) in a heterogeneous population of PAH patients.\(^\text{21}\) Both of these papers present data based on a review of the medical record only.

In a small but important Australian study, a delay in diagnosis of 47 months, which is more than 1 year greater than that previously reported by the NIH registry, is of considerable concern. In this retrospective study, a blinded interviewer asked the month and the year of initial symptom recognition and related this to the date of haemodynamic diagnosis by RHC. The authors identified three stages of delay: (i) patient-driven delays in presentation; (ii) general practitioner (GP) delays in referral; and (iii) specialist delays and multiple reviews prior to referral/presentation at a PH centre. The average time to diagnosis within this Australian study was 47 ± 34 months with approximately 1 year of this attributable to the patient time taken to recognise their need for medical help. Men had a longer time to diagnosis, with time from first medical contact to RHC almost twice that of females (24 ± 30.31 months vs 45 ± 39.95 months, respectively, \(P = 0.043\)).\(^\text{18}\) On average, patients attended a GP five times and a specialist three times prior to diagnostic RHC at a PHT centre (Fig. 3).\(^\text{16}\) Clearly a coordinated approach between the general community (patients), general practice and specialty practice is imperative to tackle this important issue.

Within the identified at risk groups a more aggressive stance may be able to be taken. Preliminary results of a large multicentre database of adult patients with systemic sclerosis, the DETECT study, were discussed extensively during the Nice meeting.\(^\text{23}\) Using a simple two-step approach utilising eight variables (forced vital capacity/diffusion capacity, past or present telangiectasia, positive serum anticardiolipin antibody, serum N-terminal pro-hormone of brain natriuretic peptide, serum urate, right atrial diameter on electrocardiogram, right atrium area and tricuspid valve regurgitation velocity on echocardiography) gave 96% sensitivity and 48% specificity in detecting RHC confirmed PHT. This approach was superior in sensitivity to the existing European Society of Cardiology/European Respiratory Society guideline. Evaluation and screening in high-risk groups are imperative for improved outcomes within these populations.

**Treatment**

Two new agents will be added and one deleted, and a stronger emphasis will be placed on evaluations for transplant in evidence-based treatment guidelines that will result from the Nice symposium. A strong recommendation of physical rehabilitation or exercise training will be made for PHT. The debate relating to exercise training will continue for some time to come, but for practical
### Table 2 Randomised controlled trials (RCT) with sequential combination therapy for pulmonary hypertension

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Initial drug</th>
<th>Combo drug</th>
<th>n</th>
<th>W</th>
<th>Aetiology (%)</th>
<th>FC (%)</th>
<th>Treatment effect</th>
<th>Δ6MWT (m)</th>
<th>Haemodynamics</th>
<th>Morbidity/motility</th>
</tr>
</thead>
<tbody>
<tr>
<td>McLaughlin et al.</td>
<td>RCT</td>
<td>Bosentan</td>
<td>Illoprost</td>
<td>67 (32 PBO, 35 INT)</td>
<td>12</td>
<td>iPAH&lt;sup&gt;6&lt;/sup&gt; CTD&lt;sup&gt;6&lt;/sup&gt; CHD&lt;sup&gt;7&lt;/sup&gt;</td>
<td>+26</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Humbert et al.</td>
<td>RCT</td>
<td>Epoprostenol</td>
<td>Bosentan</td>
<td>33 (11 PBO, 22 INT)</td>
<td>16</td>
<td>III&lt;sup&gt;48&lt;/sup&gt; IV&lt;sup&gt;48&lt;/sup&gt;</td>
<td>No effect</td>
<td>Improved</td>
<td>N/A</td>
<td>Improved</td>
<td>N/A</td>
</tr>
<tr>
<td>Simonneau et al.</td>
<td>RCT</td>
<td>Epoprostenol</td>
<td>Sildenafil</td>
<td>267 (133 PBO, 134 INT)</td>
<td>16</td>
<td>iPAH&lt;sup&gt;59&lt;/sup&gt; CTD&lt;sup&gt;4&lt;/sup&gt;</td>
<td>+28.8</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Galie et al.</td>
<td>RCT</td>
<td>Sildenafil</td>
<td>Bosentan</td>
<td>Sildenafil background (15 PBO, 14 INT)</td>
<td>28</td>
<td>iPAH CTD OHD</td>
<td>Improved (NS)</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
<td>Improved</td>
</tr>
<tr>
<td>Barst et al.</td>
<td>RCT</td>
<td>Bosentan</td>
<td>Tadalafil</td>
<td>216 (45 PBO, 45 INT (20 mg))</td>
<td>16</td>
<td>iPAH CTD OHD</td>
<td>+23</td>
<td>N/A</td>
<td>Improved</td>
<td>Improved</td>
<td>N/A</td>
</tr>
<tr>
<td>Iversen et al.</td>
<td>RCT (cross-over)</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>20 (10 PBO, 10 INT)</td>
<td>24</td>
<td>Improver</td>
<td>Improved</td>
<td>Improved</td>
<td>N/A</td>
<td>Improved</td>
<td>N/A</td>
</tr>
<tr>
<td>Hoepner et al.</td>
<td>RCT</td>
<td>Bosentan</td>
<td>Illoprost</td>
<td>40</td>
<td>12</td>
<td>iPAH CTD OHD</td>
<td>+1 (NS)</td>
<td>Improved/maintained</td>
<td>N/A</td>
<td>Improved</td>
<td>N/A</td>
</tr>
<tr>
<td>Oudiz et al.</td>
<td>RCT</td>
<td>Bosentan</td>
<td>Tadalafil</td>
<td>357 (192 on combo)</td>
<td>52</td>
<td>iPAH CTD OHD</td>
<td>i&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Improved/maintained</td>
<td>N/A</td>
<td>Improved</td>
<td>N/A</td>
</tr>
</tbody>
</table>

6MWT, 6-min walk test; Combo drug, drug added in combination therapy; FC, World Health Organization functional class; iPAH, idiopathic pulmonary arterial hypertension; NS, difference not significant; N/A, not applicable to this study; W, weeks of drug exposure in trial.
Table 3: Non-randomised trials with sequential combination therapy for PHT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Initial drug</th>
<th>Combo drug</th>
<th>n</th>
<th>W</th>
<th>Aetiology</th>
<th>FC (%)</th>
<th>Treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoeper et al</td>
<td>57 Open label</td>
<td>Bosentan</td>
<td>Sildenafil → Iloprost</td>
<td>123</td>
<td>155</td>
<td>PAH : iPAH</td>
<td>III90</td>
<td>Improved</td>
</tr>
<tr>
<td>Seyfarth et al</td>
<td>58 Open label</td>
<td>Beraprost</td>
<td>Iloprost, Iloprost</td>
<td>16</td>
<td>56</td>
<td>PAH</td>
<td>II100</td>
<td>Improved</td>
</tr>
<tr>
<td>Ghofrani et al</td>
<td>59 Open label</td>
<td>Iloprost</td>
<td>Sildenafil</td>
<td>14</td>
<td>52</td>
<td>PAH</td>
<td>II60</td>
<td>Improved</td>
</tr>
<tr>
<td>Steiner et al</td>
<td>60 Open label</td>
<td>IV Iloprost</td>
<td>Epoprostenol</td>
<td>22</td>
<td>52</td>
<td>PAH</td>
<td>II64</td>
<td>Improved</td>
</tr>
<tr>
<td>Ewert et al</td>
<td>61 Open label</td>
<td>Inhaled Iloprost</td>
<td>Iloprost</td>
<td>24</td>
<td>26</td>
<td>PAH</td>
<td>IV100</td>
<td>Improved</td>
</tr>
<tr>
<td>Hoeper et al</td>
<td>62 Open label</td>
<td>Inhaled Iloprost</td>
<td>IV Iloprost</td>
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<td>II100</td>
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<tr>
<td>Kitaoka et al</td>
<td>64 Open label</td>
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<td>PAH</td>
<td>III90</td>
<td>Improved</td>
</tr>
<tr>
<td>Porhownik et al</td>
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<td>Bosentan</td>
<td>Sildenafil</td>
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<td>12</td>
<td>PAH</td>
<td>II100</td>
<td>Improved</td>
</tr>
<tr>
<td>Lunze et al</td>
<td>66 Open label</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>11</td>
<td>56</td>
<td>PAH</td>
<td>III100</td>
<td>Improved</td>
</tr>
<tr>
<td>Ivy et al</td>
<td>67 Open label</td>
<td>Epoprostenol</td>
<td>Inhaled Iloprost</td>
<td>8</td>
<td>112</td>
<td>PAH</td>
<td>III100</td>
<td>Improved</td>
</tr>
<tr>
<td>MScot et al</td>
<td>68 Open label</td>
<td>Beraprost</td>
<td>Sildenafil</td>
<td>36</td>
<td>12</td>
<td>PAH</td>
<td>III100</td>
<td>Improved</td>
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<tr>
<td>Akg et al</td>
<td>69 Open label</td>
<td>Beraprost</td>
<td>Sildenafil</td>
<td>22</td>
<td>48</td>
<td>PAH</td>
<td>III100</td>
<td>Improved</td>
</tr>
<tr>
<td>Ivy et al</td>
<td>70 Open label</td>
<td>IV Prostanoids</td>
<td>Sildenafil</td>
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<td>167</td>
<td>PAH</td>
<td>III100</td>
<td>Improved</td>
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<tr>
<td>Chanrick et al</td>
<td>71 Open label</td>
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<td>Iloprost</td>
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<td>12</td>
<td>PAH</td>
<td>III100</td>
<td>Improved</td>
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<tr>
<td>Hoeper et al</td>
<td>73 Open label</td>
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<tr>
<td>Satchok et al</td>
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<td>III100</td>
<td>Improved</td>
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<tr>
<td>Mathai et al</td>
<td>75 Open label</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>25</td>
<td>15</td>
<td>PAH</td>
<td>II60</td>
<td>Improved</td>
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<tr>
<td>Keogh et al</td>
<td>76 Open label</td>
<td>Bosentan</td>
<td>Sildenafil</td>
<td>112</td>
<td>260</td>
<td>PAH</td>
<td>II60</td>
<td>Improved</td>
</tr>
</tbody>
</table>

6MWT, 6 min walk test; APAH, associated PAH; PBO, placebo; CHD, congenital heart disease; Combo drug, drug added in combination therapy; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; Peds, pediatric patients; PPHT, primary pulmonary hypertension; SC, subcutaneous infusion; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; W, weeks of drug exposure in trial.
purposes, exercise training (although not completely defined) will probably carry a greater weight in the new treatment algorithm for PHT patients.24,25 Earlier referral to lung/heart-lung transplant centres for patients failing therapy or presenting with severe disease will also for part of the guideline recommendations.

Studies of imatinib in combination trials have failed to show sufficient additional efficacy to warrant the additional side-effects and high cost.26 Macitentan (a new endothelin antagonist) and Riociguat (a novel drug that stimulates soluble guanylate cyclase) were proposed to be included in the evidenced-based guideline based on imminent (now published) publication of positive randomised controlled trials (RCT) and subsequent regulatory approval.27,28

Of interest, both the Macitentan and Riociguat PAH studies had a substantial numbers of patients who were already on a PAH-specific agent, nevertheless showing an additional benefit of sequentially added combination therapy. Sequential introduction of PAH specific drugs with dual and triple drug therapy in patients failing to reach therapeutic targets is also to be strongly recommended in the upcoming guidelines. Although single drug therapy is funded by PBS (according to detailed prescribing criteria by the PBS), additional selective pulmonary vasodilators are not PBS-funded. Thus, in many parts of Australia, lack of funding of additional PAH-specific medication will mean that many Australians will continue to receive care that falls short of what is recommended in current and pending international guidelines.3,29,30 There is a plethora of evidence (28 RCT/non-RCT) available for combination therapy (Tables 2 and 3). In Australia, a collaborative study demonstrated the benefits of combination therapy, albeit within the context of open label clinical practice and not in a clinical trial; however, showing substantial increased in survival for those patients able to access combination therapy.31 A similar issue with respect to lack of equitable access to therapy for Australians exists with the availability of intravenous epoprostenol, which has the strongest recommendation for PAH in patients who are New York Heart Association Functional Class IV and the only therapy to have proven benefit in terms of mortality, yet in Australia intravenous epoprostenol remains a ‘salvage therapy’ for only the lucky patients failing other therapies in centres with adequate funding of epoprostenol therapy.32 In New Zealand, the Pharmaceuticals Management Agency has successfully managed to negotiate costs in order to deliver equitable funded access to New Zealanders who require combination therapy, be that on a case by case funding request basis. Under the guidance of a panel of experts, the agency has managed to execute affordable medicines in combination for New Zealanders.

Prognosis

Most published studies of PAH-specific drugs have used 6-min walk distance as the primary end-point with the exception of the pivotal epoprostenol study that showed a survival benefit.35-42 Morbidity and mortality end-points associated with PAH have been used as secondary end-points until the recently completed large RCT studying assessing Macitentan used a composite disease progression (time to clinical worsening or morbidity mortality) as the primary end-point.36,43,44 This methodology is likely to set the benchmark for future PAH studies.

Prognosis does seem to have improved substantially in the present era of therapies, and this issue was discussed in Nice. No data exist comparing one therapy against the other; however, the evolving lines of evidence for improved survival include registries (or patients in extension of drug study), survival versus predicted survival from the NIH registry,30,43,46 improved survival versus historical controls in a single centre47 and meta-analysis of the RCT with a placebo arm48 showing overall 43% reduction of mortality in the actively treated patients.

In Australia, as part of a risk-sharing agreement between Actelion Pharmaceuticals and the PBS, a Bosentan Patient Registry was established to track survival in Bosentan-treated patients. Notwithstanding the real world issues with registry data including inevitable differences in prognosis between incident and prevalent cases, survival of the iPAH patients and the scleroderma PAH patients seemed substantially improved compared with published historical control data.49

Conclusion

The recent 5th World Symposium in Nice has allowed us to take stock of the progress made to date, review our understanding of epidemiological factors and therapy in the treatment of PHT. What is evident is that PAH remains relatively rare but more prevalent than previously thought. We have shown in Australia for the first time that all cause PHT is common and confirmed the community burden with significant mortality in untreated patients. With the availability of disease-specific drugs used according to international protocols, these outcomes are significantly improving. PAH outcomes in Australia may be further improved by earlier diagnosis and the ability to gain equitable access and adherence to guideline-recommended approaches to initial therapy and escalation to combinations of therapy.

It is also clear that most PHT is not PAH and occurs most commonly in individuals with heart disease and lung disease. It behaves the medical and scientific
community to look beyond PAH and work diligently to develop therapeutic approaches that may offer improved quality of life and survival in the much more common forms of PHT to achieve improvements in quality of life as has been documented in those patient groups with PAH amenable to PAH-specific therapy.

Importantly, in patients presenting with breathlessness of any form, PHT should be considered and ruled out. The Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ, Inc.) (http://www.phsanz.com.au) has been established to promote timely and equitable access to international standards in diagnosis and subsequent treatment through an Australian and New Zealand wide network of dedicated centres offering education and collaborative research platforms for those clinical teams looking after this difficult patient population.

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hypertension.

idiopathic pulmonary arterial hypertension.

iloprost therapy in patients with first-line inhaled iloprost to revert treatment failure of first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension.

Cor Ren Cardiol 2007; 96: 211–7.

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Pulmonary hypertension


Ejaculatory dysfunction is one of the most common male sexual disorders. The spectrum of ejaculatory dysfunction extends from premature ejaculation (PE) through delayed ejaculation (DE) to a complete inability to ejaculate, anejaculation, and includes retrograde ejaculation.

Anatomy and physiology of the ejaculatory response
The ejaculatory reflex comprises sensory receptors and areas, afferent pathways, cerebral sensory areas, cerebral motor centres, spinal motor centres and efferent pathways. Neurochemically, this reflex involves a complex interplay between central serotonergic and dopaminergic neurons, with secondary involvement of cholinergic, adrenergic, oxytocinergic and gamma aminobutyric acid (GABA) neurons. Serotonin, which inhibits emission/ejaculation, and dopamine, which promotes seminal emission/ejaculation, have emerged as key neurochemical factors.1

PE
Over the past 20–30 years, the PE treatment paradigm, previously limited to behavioural psychotherapy, has expanded to include drug treatment. Animal and human sexual psychopharmacological studies have demonstrated that serotonin and 5-hydroxytryptamine (5-HT) receptors are involved in ejaculation and confirm a role for selective serotonin re-uptake inhibitors (SSRI) in the treatment of PE.2 Multiple well-controlled, evidence-based studies have demonstrated the efficacy and safety of SSRI in delaying ejaculation, confirming their role as first-line agents for the treatment of lifelong and acquired PE.3

Epidemiology
PE has been estimated to occur in 4–39% of men in the general community4 and is often reported as the most
common male sexual disorder. There is, however, a substantial disparity between the incidence of PE in epidemiological studies that rely upon either patient self-report of PE, or inconsistent and poorly validated definitions of PE, and that suggested by community-based stopwatch studies of the intravaginal ejaculation latency time (IELT), the time interval between penetration and ejaculation. The latter demonstrates that the distribution of the IELT was positively skewed, with a median IELT of 5.4 min (range 0.55–44.1 min), decreased with age and varied between countries, and supports the notion that IELT of less than 1 min is statistically abnormal compared with men in the general Western population (Fig. 1).

Classification of PE

The population of men with PE is not homogenous and comprises lifelong (primary) and acquired (secondary) PE and has been recently expanded to include natural variable PE and premature-like ejaculatory dysfunction (Table 1).

• **Lifelong PE** is characterised by early ejaculation at every or nearly every intercourse within 30–60 s in the majority of cases (80%) or between 1 and 2 min (20%), with every or nearly every sexual partner and from the first sexual encounters onwards.

• **Acquired PE** differs in that sufferers develop early ejaculation at some point in their life having previously had normal ejaculation experiences. Acquired PE may be due to sexual performance anxiety, psychological or relationship problems, erectile dysfunction (ED), prostatitis, hyperthyroidism, or during withdrawal/detoxification from prescribed or recreational drugs.

• **Variable PE** should be regarded as a normal variation in sexual performance as the IELT is never consistently rapid but merely coincidental and situational.

• **Subjective PE** is characterised by a preoccupation with a subjective but false perception of PE by men who ejaculate with a normal IELT of 3–6 min.

Defining PE

The medical literature contains several authority-based rather than evidence-based univariate and multivariate definitions of PE. The first contemporary multivariate evidence-based definition of lifelong PE was developed in 2008 and revised in 2013 by a panel of international experts who agreed that the diagnostic criteria necessary to define PE are: time from penetration to ejaculation, inability to delay ejaculation and negative personal consequences from PE such as distress, bother, frustration and/or the development of sexual avoidance. This panel defined lifelong PE as a male sexual dysfunction characterised by ‘ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, either present from the first sexual experience or following a new bothersome change in ejaculatory latency, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy’.

This definition should form the basis for the office diagnosis of lifelong PE. It is limited to heterosexual men engaging in vaginal intercourse as there are few studies available on PE research in homosexual men or during other forms of sexual expression.

Table 1 Classification of premature ejaculation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lifelong premature ejaculation</th>
<th>Acquired premature ejaculation</th>
<th>Variable premature ejaculation</th>
<th>Subjective premature ejaculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IELT</td>
<td>Very short IELT (&lt;1–1.5 min)</td>
<td>(Very) short IELT (&lt;1.5–2 min)</td>
<td>Normal IELT (3–8 min)</td>
<td>Normal or long IELT (3–30 min)</td>
</tr>
<tr>
<td>Frequency</td>
<td>Consistent</td>
<td>(In)consistent</td>
<td>Inconsistent</td>
<td>(In)consistent</td>
</tr>
<tr>
<td>Aetiology</td>
<td>Neurobiological and genetic</td>
<td>Medical and/or psychological</td>
<td>Normal variation of ejaculatory performance</td>
<td>Psychological</td>
</tr>
<tr>
<td>Treatment</td>
<td>Medication with or without counselling</td>
<td>Medication and/or psychotherapy</td>
<td>Psycho-education, reassurance</td>
<td>Psychotherapy</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

IELT, intravaginal ejaculatory latency time.
**Aetiology of PE**

Historically, attempts to explain the aetiology of lifelong and acquired PE have included a diverse range of biological and psychological theories. Most of these proposed aetiologies are not evidence-based and are speculative at best.

Ejaculatory latency time is probably a genetically biological variable, which may differ between populations and cultures, ranging from extremely rapid through average to slow ejaculation. Some men may inherit a genetic predisposition to ejaculate with a brief latency. The increased familial occurrence of lifelong PE and the recent report that genetic polymorphism of the 5-HT transporter gene determines the regulation of the IELT support this hypothesis.9

Anxiety has been reported as a possible cause of acquired PE by multiple authors who suggest that high levels of sexual performance anxiety, and excessive and controlling concerns about sexual performance and potential sexual failure might distract a man from monitoring his level of arousal and recognising the prodromal sensations that precede ejaculatory inevitability.

Recent data demonstrate that as many as half of subjects with ED also experience acquired PE.10 Subjects with ED may either require higher levels of manual stimulation to achieve an erection or intentionally ‘rush’ intercourse to prevent early detumescence of a partial erection, resulting in ejaculation with a brief latency.

**Evaluation of men with PE**

There are several published guidelines on the management of PE.11 All focus on the following.

1 Initial identification of the true presenting complaint with a medical/sexual history as either lifelong, acquired PE, variable PE or subjective PE.
2 Identification of any obvious organic causes or comorbid disease such as ED with a focused physical examination.
3 Establishment of the optimal treatment plan.

The history should establish time of onset of PE, whether rapid ejaculation occurs on every/almost every attempt and with every partner, and the presence or absence of erectile and/or other sexual dysfunction/s. The time between penetration and ejaculation, the patient’s ability to control or delay ejaculation, and presence and extent of negative psychological consequences such as bother, distress and/or the avoidance of sexual activity are keys to the diagnosis of PE. The presence of dyspareunia, genital pain disorder, a sexual aversion disorder and/or any other sexual dysfunction in the partner should be established. A focused physical examination is mandatory in men with acquired PE and highly advisable in men with lifelong PE. Investigations are not normally required but may be indicated by the history and examination findings. Screening for prostate cancer in men aged ≥50 years with a digital rectal examination and PSA is appropriate.

**Treatment of PE**

PE treatment strategies include psychosexual counseling, daily or on-demand pharmacotherapy, either alone or in combination as part of an integrated treatment programme. Men with subjective or variable PE and normal ejaculatory latency may have unrealistic expectations of treatment based on an incorrect understanding of ‘normal’ sexual function. These men are best managed by simple psycho-education without pharmacotherapy.

**Psychosexual counselling**

The cornerstones of behavioural treatment are cognitive behavioural therapy (CBT), the Seman’s ‘stop-start’ manoeuvre and its modification proposed by Masters and Johnson, the squeeze technique. Both are based on the theory that PE occurs because the man fails to pay sufficient attention to preorgasmic levels of sexual tension. Treatment success with these behavioural approaches is relatively good in the short term, but convincing long-term treatment outcome data are lacking.12,13

CBT, especially when combined with pharmacotherapy, is an effective intervention for acquired PE related to sexual performance anxiety and a substantial proportion of men report sustained improvements on ejaculatory latency and control following cessation of pharmacotherapy.

**Pharmacological treatment**

The introduction of the serotonergic tricyclic clomipramine and the SSRI paroxetine, sertraline, fluoxetine, citalopram and fluvoxamine has revolutionised the approach to and treatment of PE (Table 2). These drugs block axonal re-uptake of serotonin from the synaptic cleft of central and peripheral serotonergic neurons by 5-HT transporters, resulting in enhanced 5-HT neurotransmission, stimulation of post-synaptic membrane 5-HT2C autoreceptors and ejaculatory delay.

**On-demand treatment with SSRI**

Dapoxetine (30 mg, 60 mg, 1–3 h prior to planned intercourse) is a rapidly absorbed, short plasma half-life SSRI specifically developed for the treatment of PE. The
Dapoxetine clinical trial programme demonstrates superiority to placebo with a dose-dependent overall fold-increase in mean IELT of 2.5–3.0 over baseline, substantial improvements in ejaculatory control, patient and partner sexual satisfaction, and reductions in personal, partner and relationship distress.14 In men with a baseline IELT of ≤30 s and more severe PE, the dose-dependent fold increase in IELT was higher at 3.4–4.3. Following treatment with dapoxetine 30 and 60 mg, 30.7% and 38.9%, respectively, regarded their PE as ‘better’ or ‘much better’. Treatment-related side-effects were uncommon and dose-dependent, and included nausea, diarrhoea, headache and dizziness.

Administration of off-label antidepressants such as the serotonergic tricyclic clomipramine and, to a lesser extent, SSRI, paroxetine, sertraline and fluoxetine 4–6 h before intercourse is modestly efficacious and well tolerated, but is associated with substantially less ejaculatory delay than daily treatment (Table 2). On-demand treatment may be used following an initial 4- to 8-week trial of daily treatment or combined with concomitant low-dose daily treatment.

**Table 2 Pharmacotherapy for premature ejaculation (PE)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Dosing instructions</th>
<th>Indication</th>
<th>Comments</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapoxetine</td>
<td>30–60 mg</td>
<td>On demand, 1–3 h</td>
<td>Lifelong PE</td>
<td>TGA-approved and &gt;50 countries worldwide</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prior to intercourse</td>
<td>Acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lifelong PE</td>
<td>Off-label</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lifelong PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50–200 mg</td>
<td>Once daily</td>
<td>Lifelong PE</td>
<td>Off-label</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20–40 mg</td>
<td>Once daily</td>
<td>Lifelong PE</td>
<td>Off-label</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.5–50 mg</td>
<td>On demand, 3–5 h</td>
<td>Lifelong PE</td>
<td>Off-label</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prior to intercourse</td>
<td>Acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.5–50 mg</td>
<td>On demand, 3–5 h</td>
<td>Lifelong PE</td>
<td>Off-label</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prior to intercourse</td>
<td>Acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25–50 mg</td>
<td>On demand, 3–5 h</td>
<td>Lifelong PE</td>
<td>Off-label</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prior to intercourse</td>
<td>Acquired PE</td>
<td>Potential risk of opiate addiction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3 sprays</td>
<td>On demand, 20–30 min</td>
<td>Lifelong PE</td>
<td>Off-label</td>
<td>High</td>
</tr>
<tr>
<td>Topical lignocaine</td>
<td></td>
<td>prior to intercourse</td>
<td>Acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>/prilocaine</td>
<td></td>
<td></td>
<td>Lifelong PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5–20 mcg</td>
<td>Patient administered</td>
<td>Lifelong PE</td>
<td>Off-label</td>
<td>Very Low</td>
</tr>
<tr>
<td>Alprostadil</td>
<td></td>
<td>intracavernous injection</td>
<td>Lifelong PE</td>
<td>Risk of priapism and corporal fibrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 min prior to intercourse</td>
<td>Acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDE5 inhibitors</td>
<td>Sildenafil</td>
<td>On demand, 30–50 min</td>
<td>Lifelong and acquired PE</td>
<td>Improved efficacy if combined with SSRI</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td>25–100 mg</td>
<td>prior to intercourse</td>
<td>in men with normal erectilefunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td></td>
<td>Lifelong and acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10–20 mg</td>
<td></td>
<td>in men with ED</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vardenafil</td>
<td></td>
<td>Improved efficacy if combined with SSRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10–20 mg</td>
<td></td>
<td>Lifelong PE</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Acquired PE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>400 mcg</td>
<td>Once daily</td>
<td>Lifelong PE</td>
<td>Off-label</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acquired PE</td>
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<td></td>
</tr>
</tbody>
</table>

ED, erectile dysfunction; PDE5, phosphodiesterase type-5; SSRI, selective serotonin re-uptake inhibitor; TGA, Therapeutic Goods Administration.

**Daily treatment with SSRI**

Daily treatment with paroxetine 10–40 mg, sertraline 50–200, fluoxetine 20–40 mg citalopram 20–40 mg and the serotonergic tricyclic clomipramine 12.5–50 mg are effective, safe and well-tolerated treatments for PE (Table 2).13 Ejaculation delay usually occurs within 5–10 days of starting treatment, but the full therapeutic effect may require 2–3 weeks of treatment and is usually sustained during long-term use.

Adverse effects are usually minor, occur in the first week of treatment, gradually disappear within 2–3 weeks and include fatigue, yawning, mild nausea, diarrhoea or perspiration. Hypoactive desire and ED are infrequently reported. Patients should be advised to
avoid sudden cessation or rapid dose reduction of SSRI that may be associated with an SSRI withdrawal syndrome.

**Topical anaesthetics**

The use of topical local anaesthetics such as lignocaine and/or prilocaine as a cream, gel or spray is well established and is moderately effective in delaying ejaculation. They may be associated with significant penile hypoanaesthesia and possible transvaginal absorption, resulting in vaginal numbness and resultant female anorgasmia unless a condom is used.

**Phosphodiesterase inhibitors**

Phosphodiesterase type-5 inhibitors (PDE5i) – sildenafil, tadalafil and vardenafil – are effective treatments for ED. Several authors have reported using PDE5i alone or in combination with SSRI as a treatment for PE. Although systematic reviews of multiple studies have failed to provide robust evidence to support a role for PDE5i in the treatment of PE, with the exception of men with PE and comorbid ED,16 recent well-designed studies do support a potential role for these agents suggesting a need for further evidence based research.17

**Other pharmacological treatments**

Treatment with daily α1-adrenoceptor antagonists such as alfuzosin and tamsulosin, on-demand tramadol or intracavernous injection of vasoactive drugs, has been reported in the literature. Tramadol is a centrally acting synthetic opioid analgesic with an unclear mode of action that is thought to include binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of re-uptake of GABA, norepinephrine, and serotonin. Most studies are poorly designed open-label trials with a wide range of efficacy. The only double-blind trial demonstrates superiority to placebo with an IELT fold-increase of 2.49, consistent with the weak serotonin re-uptake inhibitor activity of tramadol.18 The unclear safety profile and the potential for addiction discourage use of tramadol in PE clinical practice.

**Delayed ejaculation and anejaculation**

Delayed ejaculation (inhibited ejaculation, retarded ejaculation) and anejaculation are probably the least common, least studied and least understood of the male sexual dysfunctions. However, its impact is significant in that it typically results in a lack of sexual fulfilment for both the man and his partner, an effect further compounded when procreation is among the couple’s goals of sexual intercourse.

**Definition and characteristics of DE/anejaculation**

There are no clear criteria as to when a man actually meets the conditions for DE, as operationalised criteria do not exist. Given that the median IELT is 5.4 min,3 a clinician might assume that men with latencies beyond 25 or 30 min (about two standard deviations above the median) who report distress or men who simply cease sexual activity because of loss erection, exhaustion, irritation or partner request qualify for this diagnosis (Fig. 1).

Failure of ejaculation can be a lifelong problem (25%) or an acquired problem (75%). It may be global and happen in every sexual encounter or intermittent or situational. Many men with acquired DE can masturbate to orgasm, whereas others, for multiple reasons, will or cannot. Approximately 75% can reach orgasm through solitary masturbation, while the remainder fail to ejaculate.

**Pathophysiology of DE**

Any psychological or medical disease or surgical procedure that interferes with either central control of ejaculation or the peripheral sympathetic nerve supply to the vas and bladder neck, the somatic efferent nerve supply to the pelvic floor or the somatic afferent nerve supply to the penis can result in DE, anejaculation and anorgasmia. As such, the causes of DE and anejaculation are manifold (Table 3). DE because of psychogenic factors, degeneration of penile afferent nerves and Pacinian corpuscles in the ageing male, diabetic autonomic neuropathy, SSRI antidepressants and major tranquillisers, radical prostatectomy or other pelvic surgery, and spinal cord injury (SCI) are the most common causes of DE seen in clinical practice.

The ability to ejaculate may be severely impaired by SCI and is dependent upon the level and completeness of SCI.19,20 Unlike erectile capacity, the ability to ejaculate increases with descending levels of spinal injury. Less than 5% of patients with complete upper motor neuron lesions retain the ability to ejaculate. Ejaculation rates are higher (15%) in patients with both lower motor neuron lesions and an intact thoracolumbar sympathetic outflow. Approximately 22% of patients with an incomplete upper motor neuron lesion and almost all men with incomplete lower motor neuron lesions retain the ability to ejaculate. In those patients capable of successful
ejaculation, the sensation of orgasm may be absent, and retrograde ejaculation often occurs.

Evaluation of men with DE

Evaluation of men presenting with DE/anejaculation should include a full medical/sexual history, a focused physical examination including establishing whether the testes and epididymes are normal, vasa are present or absent on each side, and a DRE, determination of serum testosterone levels and any additional investigations suggested by these findings. It is also important to establish whether ejaculation is retrograde or absent, with the presence of spermatozoa in post-ejaculation first void urine indicating retrograde ejaculation.

Treatment of men with DE

Treatment should be aetiology-specific, address the issue of infertility in men of a reproductive age, and may include patient/couple psycho-education and/or psychosexual therapy, pharmacotherapy or integrated treatment. Men/partners of reproductive age undergoing pelvic surgery should be informed of the risk of infertility because of anejaculation and the availability of sperm harvesting and assisted reproductive techniques.

Psychological strategies in DE

If organic and pharmacological causes have been eliminated, referral to an expert psychosexual therapist is usually indicated to evaluate the causative psychological and behavioural issues. Psychotherapy outcomes depend on DE severity and receptiveness to engage in counselling. Numerous psychotherapeutic processes are described including sex education, reduction of goal-focused anxiety, increased genitally focused stimulation, patient role-playing, masturbatory retraining, and realignment of sexual fantasies and arousal strategies. The success of treating DE is difficult to assess from the literature as the evidence on the effectiveness of various treatments is limited, and both successful and unsuccessful case reports have been cited.21

Pharmacotherapy for DE

Drug treatment of DE or inhibited ejaculation has met with limited success (Table 4). These drugs facilitate ejaculation by either a central dopaminergic, anti-serotonergic, or oxytocinergic mechanism of action.

### Table 3 Causes of delayed ejaculation, anejaculation and anorgasmia

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ageing male psychogenic</td>
<td>Degeneration of penile afferent nerves inhibited ejaculation</td>
</tr>
<tr>
<td>Congenital</td>
<td>Mullerian duct cyst</td>
</tr>
<tr>
<td></td>
<td>Wolfian duct abnormality</td>
</tr>
<tr>
<td></td>
<td>Prune belly syndrome</td>
</tr>
<tr>
<td>Anatomic causes</td>
<td>Transurethral resection of prostate</td>
</tr>
<tr>
<td></td>
<td>Bladder neck incision</td>
</tr>
<tr>
<td>Neurogenic causes</td>
<td>Diabetic autonomic neuropathy</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td></td>
<td>Radical prostatectomy</td>
</tr>
<tr>
<td></td>
<td>Proctocolectomy</td>
</tr>
<tr>
<td></td>
<td>Bilateral sympathectomy</td>
</tr>
<tr>
<td></td>
<td>Abdominal aortic aneurysmectomy</td>
</tr>
<tr>
<td></td>
<td>Para-aortic lymphadenectomy</td>
</tr>
<tr>
<td>Infective</td>
<td>Urethritis</td>
</tr>
<tr>
<td></td>
<td>Genitourinary tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Medication</td>
<td>Alpha-methyl Dopa</td>
</tr>
<tr>
<td></td>
<td>Thiazide diuretics</td>
</tr>
<tr>
<td></td>
<td>Tricyclic and SSRI antidepressants</td>
</tr>
<tr>
<td></td>
<td>Phenothiazine</td>
</tr>
<tr>
<td></td>
<td>Alcohol abuse</td>
</tr>
</tbody>
</table>

SSRI, selective serotonin re-uptake inhibitor.

### Table 4 Drug therapy for delayed ejaculation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabergoline</td>
<td>ND</td>
<td>0.25–2 mg twice weekly</td>
</tr>
<tr>
<td>Amantadine</td>
<td>100–400 mg (2 days prior to coitus)</td>
<td>100–200 mg bid</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>60–120 mg (1–2 h prior to coitus)</td>
<td>ND</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>ND</td>
<td>4–8 mg daily</td>
</tr>
<tr>
<td>Bupropion</td>
<td>ND</td>
<td>150 mg daily or bid</td>
</tr>
<tr>
<td>Buspirome</td>
<td>ND</td>
<td>5–15 mg bid</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>4–12 mg (3–4 h prior to coitus)</td>
<td>ND</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>24 IU intranasal during coitus</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND, no data.
or a peripheral adrenergic mechanism of action. However, no drugs have been approved by regulatory agencies for this purpose, and most drugs that have been identified for potential use have limited efficacy, impart significant side-effects or are yet considered experimental in nature. Results are relatively poor in men with psychogenic DE and neuropathic DE.

**Retrograde ejaculation**

Antegrade (normal) ejaculation requires a closed bladder neck and proximal urethra. Surgical procedures or neurological disorders that compromise the bladder neck closure mechanism or innervation such as transurethral resection of the prostate (TURP), retroperitoneal lymph node dissection, multiple sclerosis or diabetic autonomic neuropathy, may result in retrograde ejaculation. Transurethral incision of the prostate results in retrograde ejaculation in as many as 45%\(^2\) of patients. Retrograde ejaculation is almost invariable following TURP.\(^3\) Retrograde ejaculation and failure of emission can be distinguished by examination of a post-masturbatory specimen of urine for the presence of spermatozoa and fructose. Retrograde ejaculation can be surgically treated with bladder neck reconstruction, but results remain consistently poor. Pharmacotherapy is ineffective in post-TURP retrograde ejaculation but has a limited role on other forms of retrograde ejaculation. Alpha-1 adrenergic receptor agonists such as pseudoephedrine and midodrine, the SNRI reboxetine or the tricyclic antidepressant imipramine, which blocks the re-uptake of noradrenaline by the axon from the synaptic cleft, have a limited role in the pharmacological treatment of retrograde ejaculation. While medical treatment may not always produce normal ejaculation, it may result in some prograde ejaculation. In patients of reproductive age, preoperative cryopreservation of semen or subsequent sperm retrieval and assisted reproductive techniques may achieve a pregnancy.

**Conclusion**

PE and DE are common complaints and are often associated with a reduced quality of sexual and overall life for both sufferer and partner. Treatment of PE with on-demand dapoxetine or daily use of off-label antidepressant SSRI or topical anaesthetic agents, alone or ideally in combination with simple psychosexual education and/or graded levels of psychosexual and relationship therapy, is an effective and well-tolerated treatment. DE and anejaculation are poorly defined disorders with multiple and diverse causative factors. Numerous psychotherapeutic treatments are described for the management of delayed or anejaculation. Drug treatment of delayed or anejaculation has met with limited success and no drugs have been evaluated in large randomised controlled trials or received regulatory approval.

**References**

15. Waldinger M. Towards evidenced based drug treatment research on premature
Colon cancer surveillance in inflammatory bowel disease: unclear gain but no psychological pain?

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Key words
inflammatory bowel disease, cancer surveillance, anxiety, risk perception, CRC.

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Abstract

Background: Surveillance for colorectal neoplasia in inflammatory bowel disease (IBD) is widely practised despite a lack of convincing mortality reduction. The psychological impact of this approach is largely unexplored.

Aim: To examine psychological well-being among IBD subjects undergoing colonoscopic surveillance for colorectal cancer (CRC).

Methods: A cross-sectional study was performed by interrogating an IBD database for subjects currently enrolled in colonoscopic surveillance programmes. Identified surveillance subjects were age- and gender-matched with IBD control subjects not meeting surveillance criteria. Subjects were mailed a questionnaire including demographic details, the Short Form 36 (SF-36) survey to assess quality of life, the Spielberger State-Trait Personality Inventory, the Multidimensional Health Locus of Control, and a Risk Perception Questionnaire.

Results: One hundred and thirty-nine of 286 (49%) subjects responded, 53% male, 46% Crohn disease. Fifty-six per cent respondents were in the surveillance group. Surveillance subjects were older (55.4 vs 51.1 years; \( P = 0.048 \)) with longer disease duration, but otherwise had comparable demographics with controls. Overall, quality of life was not significantly different between cohorts (mean SF-36 63.82 vs 65.48; \( P = 0.70 \)). Groups did not differ on any locus of control classification (\( P = 0.52 \)), nor was there any difference between mean scores on ‘state’ subscales of the Spielberger State-Trait Personality Inventory: anxiety (\( P = 0.91 \)), curiosity (\( P = 0.12 \)), anger (\( P = 0.81 \)) or depression (\( P = 0.70 \)). Both groups grossly overestimated their perceived lifetime risk of CRC at 50%, with no difference between surveillance and control subjects (\( P = 1.0 \)).

Conclusions: Enrolment in colonoscopic colon cancer surveillance does not appear to impair psychological well-being in individuals with IBD despite longer disease duration. IBD patients overestimate their risk of CRC.
**Introduction**

Colonoscopic surveillance for dysplasia and colorectal carcinoma in inflammatory bowel disease (IBD) is widely practised. While Cochrane review data suggest such surveillance promotes the earlier detection of colorectal cancer (CRC), no clear mortality reduction has yet been demonstrated.\(^1\) Moreover, several population-based IBD cohort studies have suggested no excess in CRC risk compared with the population within which they reside.\(^2\)\(^-\)\(^4\) This questionable long-term benefit renders the psychological impact of screening an important consideration in justifying ongoing surveillance in the future, and at present, this risk-benefit ratio remains largely unexplored in IBD.

In screening for other cancers such as breast cancer by mammography, patients with increased perceived susceptibility to breast cancer experience significantly increased psychological distress that is not alleviated by screening. One study demonstrated the greatest level of post-screening cancer-specific concerns in women having false-positive screening tests, suggesting the potential for deleterious psychological outcomes of screening.\(^5\) A contrasting investigation of the psychological effect of breast cancer screening in patients post-radiation for Hodgkin lymphoma suggested a positive effect on psychological parameters, demonstrating that after screening, women had improved knowledge and a significant sense of reassurance.\(^6\)

Much research in CRC focuses on hard outcomes such as detection rate, mortality and cost-effectiveness. Minimal published data address the potential psychological effects of colonoscopic surveillance, important as such effects may impact upon patient adherence and ultimately the long-term efficacy of this practice in reducing CRC. Existing data regarding ‘intangible’ costs and benefits of CRC screening come from small studies.

The purpose of our study was to address this knowledge gap in the risk benefit ratio of colonoscopic CRC surveillance in IBD by assessing the psychological impact of this practice in a setting where evidence of overwhelming benefit from surveillance has not yet been shown.

**Aim**

To examine whether psychological wellbeing is impaired in individuals with IBD undergoing CRC surveillance using colonoscopy, compared with IBD subjects not yet enrolled in a surveillance programme. Specifically we will examine quality of life (QOL), the locus of control to which IBD subjects attribute health outcomes, psychological state and trait including anxiety, depression, anger and curiosity, and perception of CRC risk.

**Methods**

A cross-sectional study was performed by interrogation of a tertiary hospital IBD database including public and private patients currently enrolled in colonoscopic CRC surveillance programmes based on ulcerative colitis (UC) or colonic Crohn disease (CD) duration greater than or equal to 8 years, with or without coexistent primary sclerosing cholangitis (PSC)\(^7\) of any duration. These individuals had received counselling by their treating specialist regarding the increased risk of CRC associated with long-standing colitis or coexisting PSC and had consented to colonoscopic surveillance. Subjects in this cohort could be anywhere in the surveillance cycle, ranging from having recently had a colonoscopy to immediately awaiting one.

Identified surveillance subjects were gender-matched and age-matched as closely as possible with other IBD patients in the database not yet meeting surveillance criteria based on shorter disease duration or refusal of colonoscopic surveillance. All eligible subjects were simultaneously mailed a written questionnaire, comprising demographics questions along with psychological surveys to assess QOL, health locus of control, psychological state and trait characteristics, and risk perception with regard to CRC.

**Demographics**

Details such as age, gender, country of origin, primary language spoken, occupational status, car and house ownership, highest educational qualification and marital status were sought. A limited amount of data was available on the hospital database regarding extent of disease and coexistence of PSC, and these data were gathered where possible and contributory.

**Bowel symptoms**

Current bowel symptoms were sought in questions regarding constipation, diarrhoea, wind, abdominal pain, incontinence, rectal bleeding and haemorrhoids to indicate level of disease activity at the time of questionnaire completion.

**Quality of life: Short Form 36 (SF-36)**

The 4-week SF-36 questionnaire\(^8\) was used to assess QOL, divided into mental and physical components, and
Aiming to assess the level of limitation of daily activities imposed by symptoms over the past 4 weeks, subjects were asked to respond to 36 questions that yield scores in eight domains comprising physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. A score out of 100 is calculated for each subject in each domain, then in overall physical and mental domains, where 100 indicates a better state of health or well-being, and lower scores are associated with reduced QOL. Australian population SF-36 data were used to compare QOL in overall physical and mental domains with each IBD cohort.

Locus of control

The Levenson Multidimensional Locus of Control Scale\textsuperscript{10} was incorporated into the questionnaire to determine the tendency of individuals to attribute control of health events to their own actions, that of others or to chance alone, and to compare these attributes between surveillance and control cohorts. This test asks subjects to rate numerically attitudinal statements according to how much they agree (+1 to +3) or disagree (−1 to −3) with each statement. Different forms of this test are available based on characteristics of the groups to be compared, and Form C\textsuperscript{10} was applied in this study as this is a condition-specific measure of locus of control, and all subjects in our study had IBD. Of the 18 statements, six indicate an ‘Internal’ locus of control, six a ‘Powerful Others’ Locus (in the case of Form C, the powerful others being health professionals), and a further six items assess a ‘Chance’-related locus of control. A score is calculated for each subject on each locus to determine to which of the three they are most likely to attribute health events.

Anxiety, depression, anger and curiosity

The Spielberger State-Trait Personality Inventory (STPI)\textsuperscript{11,12} was used to assess and compare depressive symptoms, anxiety, anger and curiosity between cohorts in both the immediate (state) and long term (trait or personality characteristic). Subjects were asked to respond to 80 questions in total using a scale of 1–4 in terms of how they feel at that moment in time and also in the longer term (ranging from almost never to almost always) in response to a series of attitudinal statements. The lowest score is 20, and the highest score is 80, higher scores indicating a greater level of anxiety, depression, anger or curiosity. This test has been shown to be reliable and valid.\textsuperscript{11}

Risk perception

A Risk Perception Questionnaire\textsuperscript{14} included nine questions assessing subject perception of risk likelihood, susceptibility and severity regarding CRC. Subjects’ perceptions of surveillance efficacy and ease were also sought, along with their stage of readiness for surveillance participation (Table 7). All answers took the form of categorical variables or percentage estimation.

Questionnaires returned within 3 months were analysed, with one reminder letter sent after 1 month if no response was received.

Ethical considerations

This study was approved by the Flinders Clinical Research Ethics Committee of Flinders University, South Australia. Informed consent on behalf of participants was implied in the form of a completed and returned questionnaire.

Statistics

Chi-squared and Fisher’s exact test were used to compare groups on categorical variables. Depending on normality of data distribution, Mann–Whitney or \(t\) tests were used to compare groups on continuous variables. Significance was reported at the 0.05 level.

Results

Of 143 subjects in each group, surveillance subjects were more likely to complete the questionnaire (78/143 (56%) vs 61/143 (44%), \(P = 0.058\)) with an overall response rate of 139/286 (49%). Fifty-three per cent of respondents were male, and 46% had CD. Males and females did not differ in the likelihood of completing the survey (\(P = 0.19\)), and disease type also did not appear to influence study participation (\(P = 0.11\)).

Demographics

In comparing surveillance subjects with controls, surveillance subjects were significantly older (55.4 vs 51.1 years; \(P = 0.048\)) but had comparable IBD type, marital status, education, language spoken and employment status to the IBD control subjects (Table 1). By definition, the surveillance subjects had longer mean disease duration than IBD controls (21.4 (range 8–50) vs 5.2 (range 1–12) years, \(P < 0.0001\)).

Two subjects were known to have coexisting PSC, both in the surveillance group. Four subjects in the IBD control group were not undergoing surveillance despite disease duration greater than 8 years, two as they had proctitis only, and a further two who refused the offer of surveillance.
Bowel symptoms

With regard to bowel symptoms, diarrhoea was reported more commonly among IBD control subjects ($P = 0.043$). Consistent with this, IBD controls also demonstrated a trend towards more abdominal pain ($P = 0.057$). No other difference in bowel symptoms was observed (Table 2).

Quality of life

Overall, QOL was no different between surveillance subjects and IBD controls (SF-36 mean 63.82 vs 65.48, respectively; $P = 0.70$); nor were there any differences within each QOL domain nor for physical or mental component summary scores (PCS and MCS) (Table 3). When analysing males alone, overall QOL did not significantly differ between surveillance subjects and IBD controls, nor in any individual domain of QOL, and a similar finding was noted when comparing female surveillance subjects and IBD controls with one another (Table 4). PCS and MCS for the age- and gender-matched Australian population are similar to these findings in IBD subjects and are summarised in Table 4.
Locus of control

Groups did not differ in mean score on any locus of control classification (Internal, Powerful Others and Chance Locus of Control, all $P = 0.52$) (Table 5), indicating a similar perspective for the attribution of health events by the cohorts.

Anxiety, depression, anger and curiosity

There was no demonstrated difference between IBD cohorts in mean scores on ‘state’ subscales of the STPI: anxiety ($P = 0.91$), curiosity ($P = 0.12$), anger ($P = 0.81$) and depression ($P = 0.70$). Mean Spielberger ‘trait’ scores for these four parameters were within expected normative ranges in both surveillance and control IBD groups, with no significant difference between IBD groups (Table 6).

Risk perception

Interestingly, despite the age difference between groups, CRC Risk Perception did not differ between surveillance and control subjects ($P = 1.0$), with both IBD groups

Table 3 Median score on SF-36 subscales by cohort

<table>
<thead>
<tr>
<th>SF-36 domain</th>
<th>Median (IQR)</th>
<th>z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD surveillance, n = 78</td>
<td>IBD controls, n = 61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>90 (70–95)</td>
<td>85 (70–95)</td>
<td>−0.520</td>
</tr>
<tr>
<td>Role physical</td>
<td>75 (25–100)</td>
<td>75 (25–100)</td>
<td>−0.338</td>
</tr>
<tr>
<td>Pain</td>
<td>72 (41–84)</td>
<td>62 (41–84)</td>
<td>−0.930</td>
</tr>
<tr>
<td>General health</td>
<td>52 (35–72)</td>
<td>53.5 (27.7–69.2)</td>
<td>−0.632</td>
</tr>
<tr>
<td>Vitality</td>
<td>50 (25–70)</td>
<td>50 (30–65)</td>
<td>−0.466</td>
</tr>
<tr>
<td>Social functioning</td>
<td>75 (62.5–100)</td>
<td>75 (62.5–100)</td>
<td>−0.262</td>
</tr>
<tr>
<td>Role emotional</td>
<td>100 (33.3–100)</td>
<td>100 (66.6–100)</td>
<td>0.007</td>
</tr>
<tr>
<td>Mental health</td>
<td>76 (60–84)</td>
<td>68 (60–80)</td>
<td>−1.251</td>
</tr>
<tr>
<td>Physical component summary</td>
<td>46.9 (36.2–53.1)</td>
<td>44.2 (38.1–52.9)</td>
<td>−0.529</td>
</tr>
<tr>
<td>Mental component summary</td>
<td>49.1 (38.6–54.2)</td>
<td>48.6 (40.1–53.7)</td>
<td>−0.317</td>
</tr>
</tbody>
</table>

Table 4 Quality of life by SF-36: physical and mental components by gender

<table>
<thead>
<tr>
<th>SF-36 component</th>
<th>Median (IQR)</th>
<th>z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD surveillance, n = 33</td>
<td>IBD controls, n = 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component</td>
<td>46.1 (35.9–53.1)</td>
<td>43.9 (38.6–52.6)</td>
<td>0.500</td>
</tr>
<tr>
<td>Mental component</td>
<td>49 (37.6–52.9)</td>
<td>48.7 (39.1–54.5)</td>
<td>0.534</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component</td>
<td>48.8 (36.5–53.1)</td>
<td>44.7 (33.9–53.6)</td>
<td>0.595</td>
</tr>
<tr>
<td>Mental component</td>
<td>51.8 (38.9–55.9)</td>
<td>48.6 (41.6–52.8)</td>
<td>0.590</td>
</tr>
<tr>
<td>Australian population age-matched mean values$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component</td>
<td>46.6</td>
<td>49.7</td>
<td></td>
</tr>
<tr>
<td>Mental component</td>
<td>50.6</td>
<td>50.3</td>
<td></td>
</tr>
</tbody>
</table>

Table 5 Multidimensional locus of control mean scores by cohort

<table>
<thead>
<tr>
<th>Locus type</th>
<th>Mean (SD)</th>
<th>t</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD surveillance</td>
<td>IBD controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal locus of control</td>
<td>5.84 (0.67)</td>
<td>6.07 (0.79)</td>
<td>−0.441</td>
<td>132</td>
</tr>
<tr>
<td>Powerful others locus of control</td>
<td>4.91 (0.57)</td>
<td>4.35 (0.56)</td>
<td>0.825</td>
<td>132</td>
</tr>
<tr>
<td>Chance locus of control</td>
<td>5.30 (0.61)</td>
<td>4.99 (0.65)</td>
<td>1.051</td>
<td>131</td>
</tr>
</tbody>
</table>

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grossly overestimating their perceived lifetime risk of CRC at 50%. A high proportion of subjects in both groups, however, agreed that surveillance would reduce their CRC risk (93.4% SS vs 89.8% CS, \( P = 0.53 \)) (Table 7).

**Discussion**

This is the largest study to our knowledge examining psychological parameters in IBD subjects undergoing versus not undergoing colonoscopic surveillance for CRC. Given the data addressing surveillance utility in this population remains debatable, it is crucial to exclude the possibility of psychological harm as a result of such surveillance.

We have demonstrated no evidence of psychological harm or benefit among IBD patients undergoing surveillance colonoscopy compared with those not yet enrolled in a surveillance programme. A striking and novel finding was that subjects in both surveillance and control groups vastly overestimated their lifetime risk of CRC at 50%, whereas current data suggest the actual risk of CRC in colitis (UC or CD) is 2% after 10 years, 8% after 20 years and 18% after 30 years of disease.\(^{15}\)

This phenomenon of exaggerated risk perception has been observed in other endoscopic surveillance programmes. Shaheen et al.\(^{14}\) reported that 63% and 38% of patients undergoing surveillance for Barrett oesophagus overestimated their 1 year and lifetime risk of cancer respectively. Such risk overestimation has been associated with increased anxiety in other surveillance settings,\(^{16}\) but interestingly in our study, surveillance was not associated with increased short- or long-term anxiety when compared with non-surveillance IBD subjects and also compared with general population norms. This may reflect confidence in the surveillance programme, as a high proportion of our subjects felt that participating in surveillance colonoscopy would reduce their risk of cancer. It is also possible that participation bias is relevant here such that the 49% of invitees who responded may have done so as they are more comfortable with surveillance practices and the risk confrontation this entails.

Other studies addressing the psychological effects of cancer surveillance have produced mixed results. A Swedish study assessing anxiety and coping ability before and after surveillance colonoscopy in 41 UC subjects

### Table 6  
Spielberger State-Trait Personality Inventory

<table>
<thead>
<tr>
<th>Trait (SD)</th>
<th>IBD surveillance, n = 78</th>
<th>IBD controls, n = 61</th>
<th>t</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>State anxiety</td>
<td>18.8 (4.1)</td>
<td>18.9 (3.5)</td>
<td>−0.116</td>
<td>136</td>
<td>0.908</td>
</tr>
<tr>
<td>State curiosity</td>
<td>26.2 (7.1)</td>
<td>24.6 (4.8)</td>
<td>1.55</td>
<td>131</td>
<td>0.122</td>
</tr>
<tr>
<td>State anger</td>
<td>12.1 (5.1)</td>
<td>11.9 (3.7)</td>
<td>0.248</td>
<td>136</td>
<td>0.805</td>
</tr>
<tr>
<td>State depression</td>
<td>17.7 (5.9)</td>
<td>18.1 (5.4)</td>
<td>−0.385</td>
<td>132</td>
<td>0.701</td>
</tr>
<tr>
<td>Trait anxiety</td>
<td>20.6 (6.3)</td>
<td>20.3 (5.1)</td>
<td>0.260</td>
<td>135</td>
<td>0.796</td>
</tr>
<tr>
<td>Trait curiosity</td>
<td>27.6 (5.9)</td>
<td>27.6 (5.3)</td>
<td>−0.067</td>
<td>134</td>
<td>0.946</td>
</tr>
<tr>
<td>Trait anger</td>
<td>15.8 (9.8)</td>
<td>15.2 (5.1)</td>
<td>0.393</td>
<td>137</td>
<td>0.695</td>
</tr>
<tr>
<td>Trait depression</td>
<td>18.8 (5.3)</td>
<td>18.9 (4.3)</td>
<td>−0.163</td>
<td>131</td>
<td>0.868</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease; SD, standard deviation.

### Table 7  
Risk perception of colorectal cancer in IBD surveillance versus control subjects

<table>
<thead>
<tr>
<th>Statement</th>
<th>Frequency (%)</th>
<th>IBD surveillance, n = 78</th>
<th>IBD controls, n = 61</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of colorectal cancer if not participate in surveillance</td>
<td>It is likely</td>
<td>54 (70.1)</td>
<td>38 (63.3)</td>
<td>0.401</td>
</tr>
<tr>
<td>How much more likely are you to suffer from colorectal cancer than the average person of the same gender and age</td>
<td>More likely than others</td>
<td>64 (82.1)</td>
<td>46 (76.7)</td>
<td>0.679</td>
</tr>
<tr>
<td>How serious would it be if you were to suffer from colorectal cancer</td>
<td>Serious</td>
<td>72 (93.5)</td>
<td>54 (90)</td>
<td>0.534</td>
</tr>
<tr>
<td>I am confident I can participate in colorectal cancer surveillance</td>
<td>Agree</td>
<td>73 (94.8)</td>
<td>52 (88.1)</td>
<td>0.208</td>
</tr>
<tr>
<td>I will find it difficult to participate</td>
<td>Disagree</td>
<td>62 (81.6)</td>
<td>44 (77.2)</td>
<td>0.534</td>
</tr>
<tr>
<td>Surveillance recommendations will reduce my risk</td>
<td>Agree</td>
<td>71 (93.4)</td>
<td>53 (89.8)</td>
<td>0.533</td>
</tr>
<tr>
<td>No matter what I do the risk remains the same</td>
<td>Disagree</td>
<td>62 (81.6)</td>
<td>49 (83.1)</td>
<td>0.824</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease.
found no difference in these parameters when compared with UC subjects not yet eligible for surveillance. However, a population-based US study suggested that people given ‘information overload’ about their cancer risk as part of screening or surveillance were more likely to report higher anxiety levels, whereas another study demonstrated improvement in the mental health and vitality domains of QOL after colonoscopic screening for CRC. This balance of positive and negative influences upon anxiety levels may result in the seemingly neutral effect of surveillance seen in our cohort.

QOL also appeared to be unaffected by surveillance in our study. Very few studies have investigated QOL specifically in IBD populations undergoing surveillance colonoscopy. One recent prospective study included a subset of IBD patients in a QOL analysis pre- and post-colonoscopy for a variety of indications using SF-36 and found no difference in overall QOL pre- and post-procedure. Interestingly, the decrease in the QOL domain of physical functioning reported in non-IBD subjects 1 month after the procedure was not observed in the IBD subset.

It is interesting that both IBD cohorts in our study had comparable QOL scores with the general Australian population. A large Norwegian study measuring QOL by SF-36 found significantly reduced QOL in six of eight dimensions for UC subjects and seven of eight dimensions among Crohn’s subjects compared with the general population, this difference further exaggerated in IBD patients with active disease. This may reflect participation bias in our cohort, whereby those with poorer QOL may have elected not to return the survey.

Subjects in both IBD cohorts in this study tended to overestimate vastly their lifetime CRC risk. This overestimation may prove advantageous, as this characteristic has been shown in several studies to improve adherence to cancer screening programmes. Whether increased participation results in better outcomes is debatable, however, as a 2010 Netherlands study demonstrated that many IBD patients had limited understanding regarding surveillance, and that 70% of those present at an information session would refuse colectomy if dysplasia were found at colonoscopy. Interestingly, subjects in this study estimated their CRC risk at 25%, half of that estimated by our cohorts.

Cancer risk perception has been shown to be subject to various factors, of which genetic risk and personal history of cancer appear to be the most important. Predictors of higher perceived risk of CRC in a large population-based study included being female, younger, having a positive family history of CRC, more bowel symptoms, poorer perceived health and higher anxiety levels. A study specific to IBD subjects identified predictors of higher perceived risk to be more than five IBD flares per year, knowing someone with CRC and being female. Interestingly, disease duration and type were not influencing variables in this study, similar to our finding of comparable risk perception in cohorts with contrasting disease duration and subject age. Our cohorts may have differed from each other in disease activity with IBD control subjects reporting more bowel symptoms, but this again did not appear to affect risk perception.

Cognitive factors also influence risk perception. Those who believe CRC is not a preventable disease have higher levels of perceived risk, and it is interesting to note that neither of our IBD cohorts demonstrated low internal locus of control, a characteristic likely to increase perceived cancer risk. An inverse relationship between spirituality and risk perception has been found in two studies, such that spiritual coping may reduce cancer risk perception, although an assessment of this as an example of an external locus of control was not undertaken in our cohorts.

This study is limited by its cross-sectional nature and thus data regarding timing within the surveillance cycle were not gathered, and this may have influenced results. It was also beyond the scope of this survey to undertake rigorous assessment of disease activity, medication regimen and adherence, disease severity, as well as family history of CRC, all of which may influence the psychological parameters assessed.

Conclusion

Colonoscopic CRC surveillance does not appear to impair or improve psychological well-being in patients with IBD. Our findings do not impose ethical barriers on continued surveillance at present, while more convincing mortality reduction data attributable to this practice are awaited. Clinicians have an opportunity to reduce CRC rates by promoting optimal disease control, while addressing the tendency towards overestimation of cancer risk in IBD patients by provision of accurate, numerical risk estimates as part of the routine clinical encounter in a way that is easy for patients to understand.
Mountfield et al.

References


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Health status, late effects and long-term survivorship of allogeneic bone marrow transplantation: a retrospective study

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Abstract

Background: Survival after allogeneic haemopoietic stem cell transplantation (allo-HSCT) has improved because of advancements in allo-HSCT. Allo-HSCT has been performed in Australia since the late 1970s. However, there are few published data about health problems of allo-HSCT survivors in Australia.

Aims: Identify health issues in long-term survivors of allo-HSCT in an Australian centre to manage better and prevent long-term complications.

Methods: The health records of all patients of allo-HSCT in a single centre from January 2000 to December 2007 and survived beyond 2 years were assessed.

Results: Ninety-nine of the 200 allo-HSCT patients survived beyond 2 years, and the median time from allo-HSCT was 74 months. Twenty-eight per cent died at a median of 37 months after allo-HSCT because of relapsed malignancy (12%), stroke (1%), infection (3%), chronic graft versus host disease (9%), secondary malignancy (2%) and unknown cause (1%). Ninety-one per cent reported one or more chronic health conditions. Health issues were chronic graft versus host disease (70%); respiratory (66%), ophthalmic (40%), bone (33%), and renal (26%) problems; and malignancies (14% skin, 3% solid organ). Seventy-nine per cent resumed vocation at full or reduced capacity 2 years after allo-HSCT. Clinicians identified 40% with quality of life (QOL) issues, but survivors’ self-reported QOL was comparable with the general Australian population.

Conclusion: This study shows that allo-HSCT patients are living with high burdens of chronic diseases that warrant lifelong surveillance and engagement with healthcare. Structured, multi-disciplinary care as recommended by published guidelines for allo-HSCT survivors may reduce long-term effects and improve their outcomes.

Introduction

Allogeneic haemopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment for selected malignant and non-malignant conditions. Allo-HSCT is now possible for an increasing number of diseases and patients. Survivorship continues to improve through advancement in histocompatibility testing, conditioning regimens, supportive care and management of graft versus host disease (GVHD). The Australian Blood and Marrow Transplant Recipient Registry reported that overall survival for allo-HSCT patients improved from 21% in 1992–1997 to 40% in 1998–2005. A study that considered long-term Australian and New Zealand allo-HSCT patients’ annual mortality rates found that relative survival was 99.5% of the general population between 6 and 10 years post-transplant. A US centre recently reported that patients who survived over 5 years after allo-HSCT without disease recurrence had a high probability of surviving a further 15 years, although mortality remained higher than the age-matched normal population. These studies indicate that disease burdens remain high in allo-HSCT survivors, and reduction in long-term morbidity and mortality should be key measures of success. There will be more patients living with chronic effects of allo-HSCT; quality of life (QOL) and late (>2 years) complications are strategic foci in allo-HSCT services.

Early and long-term post-transplant complications are well described, and incidences of late transplant complications gathered from large European and North American studies are readily available. International
guidelines have been recently published pertaining to screening and preventative practices.8,9

Allo-HSCT began in Australia and New Zealand in the early 1970s. However, there are few published local data pertaining to long-term outcomes. One-third of our allo-HSCT patients live over 100 km from our hospital, which reflects Australia’s sparsely populated demographics.

In this study, we sought to identify survivorship issues, such as organ dysfunction, secondary malignancies, emotional health, return to work or study and social reintegration after transplantation in our allo-HSCT service which may help to manage better preventable long-term complications.

**Methods**

**Patients and data collection**

This was a single-centre, retrospective study of all allo-HSCT patients surviving at least 2 years after transplantation. Data were collected to 30 June 2012 from all patients who underwent allo-HSCT between January 2000 and December 2007. These include chronic graft versus host disease (cGVHD), non-malignant late effects of allo-HSCT, new malignancies, psychosocial and QOL issues. This study was approved by our institute’s Human Ethics Committee.

**Results**

**Characteristics of the study population**

There were 200 allo-HSCTs performed between January 2000 and December 2007. Patients who died within 2 years of their transplant (n = 80) were excluded. To reduce the bias of selective reporting, we excluded patients not in contact with the allo-HSCT team due to discharge to primary care physician or haematologist (n = 12), non-attendance (n = 2), relocation overseas (n = 2) and incomplete data (n = 5).

The study population was 99 patients. The median age was 43 years (range 18–64 years). There were 55 men and 44 women.

All allo-HSCTs performed during the study period were first transplantations. The median time from diagnosis to allo-HSCT was 50.5 months (range 24–115 months). The median follow-up period to the point of data collection was 74 months (range 25–141 months). Please refer to Table 1.

**Survival**

The overall survival probability was 60% at 140 months using Kaplan–Meier analysis. Twenty-eight patients died from relapsed malignancy (12), stroke (1), infection (3), cGVHD (9), secondary malignancy (2) and unknown cause (1).

**cGVHD**

Sixty-nine (70%) patients were diagnosed with cGVHD. The only statistically different characteristic between patients with and without cGVHD was age; the median age of patients with cGVHD was 19 years older (P = 0.01). The commonest systems involved by cGVHD were musculoskeletal and skin. Forty-eight patients (48%) remained on treatment for cGVHD during the study. Please refer to Table 2, 3 and 4 for a summary.

**Non-malignant late effects of HSCT**

Please refer to Table 5 for a summary.

**Cardiovascular system (CVS)**

Forty-seven percent (28 of 59) had CVS late effects: coronary artery disease (n = 2), anthracycline-induced cardiomyopathy (n = 1), hypertension (n = 21), aortic dissection (n = 1), stroke (n = 1) and valvular heart disease (n = 2).

**Endocrine system**

Six percent (4 of 71) were hypothyroid and on thyroid replacement therapy.

*Diabetes Mellitus:* Four per cent (2 of 55) experienced steroid induced diabetes that resolved after cessation of corticosteroids.

*Hypogonadism:* Thirty-two per cent (21 of 66) had normal follicle stimulating hormone, luteinising hormone and either oestrogen or testosterone levels for age and gender. Sixty-eight per cent (45 of 66) patients were hypogonadal (34 women, 11 men). Twenty-one women and three men were on hormonal replacement therapy (HRT).

**Fertility, genital tract and reproduction**

No patients conceived after allo-HSCT. There were 20 women under the age of 40 years in the study and two underwent in vitro fertilisation.

Ten females reported one or more symptoms in their genitalia. cGVHD symptoms were vaginal stenosis (n = 2), cervical stenosis (n = 1) and vaginal scars and lichen planus-like features (n = 5). Other symptoms involving the genitalia were vaginal dryness, pain, dyspareunia and vulvovaginitis.
Table 1 Demographics of study population

<table>
<thead>
<tr>
<th></th>
<th>AML (n = 23)</th>
<th>ALL (n = 15)</th>
<th>CML (n = 17)</th>
<th>MDS (n = 11)</th>
<th>CLL (n = 5)</th>
<th>NHL (n = 16)</th>
<th>HL (n = 3)</th>
<th>MM (n = 7)</th>
<th>SAA (n = 2)</th>
<th>Study population (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at transplant (years)</td>
<td>42</td>
<td>28</td>
<td>38</td>
<td>46.5</td>
<td>53</td>
<td>49</td>
<td>30</td>
<td>51</td>
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<td>68</td>
<td>77</td>
<td>71</td>
<td>69</td>
<td>76.5</td>
<td>49</td>
<td>72</td>
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<td></td>
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<td>MUD</td>
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<td>8</td>
<td>10</td>
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<td>5</td>
<td>3</td>
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<td>46</td>
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<td>Cord</td>
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<td>0</td>
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<td>1</td>
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<td>2</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>10</td>
<td>1</td>
<td>3</td>
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</tr>
<tr>
<td>Bu/Cy</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>29</td>
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<td>Cy/TBI</td>
<td>8</td>
<td>7</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>36</td>
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<tr>
<td>Flu/Mel</td>
<td>5</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>3</td>
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<td>28</td>
</tr>
<tr>
<td>Flu/TBI</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
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<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>28</td>
</tr>
</tbody>
</table>

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BM, bone marrow; Bu/Cy, busulfan/cyclophosphamide; CLL, chronic lymphocytic leukaemia; CML, chronic myelogenous leukaemia; Cy/ATG, cyclophosphamide/anti-thymocyte globulin; Cy/TBI, Cyclophosphamide/total body irradiation; Flu/Mel, fludarabine/melphalan; Flu/TBI, fludarabine/total body irradiation; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; MUD, matched unrelated donor; NHL, non-Hodgkin lymphoma; PBSC, peripheral blood stem cell; RIC, reduced intensity conditioning; SAA, severe aplastic anaemia.
One male patient reported decreased libido and two reported erectile dysfunction.

**Gastrointestinal tract (GIT) and hepatobiliary tract**

Twenty-two per cent (22 of 99) experienced GIT disturbances. cGVHD manifestations were oesophageal web (n = 2), oesophageal strictures (n = 3), chronic diarrhoea (n = 4) and anorexia (n = 1). Other GIT symptoms were gastro-oesophageal reflux (n = 4), perianal fistulae (n = 2), dysphagia without anatomical cause (n = 2), small intestinal stenosis (n = 1), protein losing enteropathy (n = 1) and irritable bowel syndrome (n = 2).

Eleven patients had hepatic cGVHD and were treated with immunosuppression.

Liver enzymes and ferritin levels were measured to screen for hepatobiliary complications. Twenty patients had abnormal liver enzymes, predominantly with elevated gamma-glutamyl transferase and alkaline phosphatase. Thirty-two patients had elevated ferritin levels, only one required therapeutic venesections.

**Musculoskeletal and soft tissue**

All patients were prescribed vitamin D and calcium supplementation. Fifty-two per cent (33 of 64) had reduced bone mineral density (BMD) measured by dual energy X-ray absorptiometry. Eleven patients were prescribed bisphosphonates, including six patients who continued prednisone for cGVHD. Four patients experienced minimal trauma fractures and three suffered avascular necrosis of joints.

Twenty-eight per cent (28 of 99) patients reported one or more soft tissue symptoms: cramps (n = 12), muscle tightness (n = 8), sclerodermatous skin changes causing joint contractures (n = 4), arthralgia (n = 3) and joint stiffness (n = 4).

**Immunodeficiency and infections**

Howell Jolly bodies as a surrogate for functional hyposplenism were found in nine (9%) patients.

Thirty patients remained on prophylactic antimicrobials, including 21 patients who remained on immunosuppressants for cGVHD. One hypogammaglobulinaemic patient who was being treated for cGVHD died of sepsis 48 months after allo-HSCT. Other infective late effects were recurrent lower respiratory tract infections (n = 2), herpes zoster virus reactivation (n = 2), recurrent herpes simplex virus reactivation (n = 1) and mucormycosis (n = 1).

**Renal tract**

Twenty-six per cent (26 of 99) had chronically abnormal estimated glomerular filtration rate on serum

---

**Table 2** Characteristics of patients with and without chronic graft versus host disease (cGVHD)

<table>
<thead>
<tr>
<th></th>
<th>cGVHD (n = 69; 70%)</th>
<th>No cGVHD (n = 30; 30%)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>54 years</td>
<td>35 years</td>
<td>0.01†</td>
</tr>
<tr>
<td>Male : female</td>
<td>1.2</td>
<td>1.1.5</td>
<td>0.6‡</td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>22 (32%)</td>
<td>5 (17%)</td>
<td>0.1§</td>
</tr>
<tr>
<td>Alive</td>
<td>47 (68%)</td>
<td>25 (83%)</td>
<td></td>
</tr>
<tr>
<td>Median time from HSCT Conditioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloablatite</td>
<td>43 (62%)</td>
<td>22 (73%)</td>
<td>0.4‡</td>
</tr>
<tr>
<td>RIC</td>
<td>26 (38%)</td>
<td>8 (27%)</td>
<td></td>
</tr>
<tr>
<td>Stem cell source</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>61 (88.4%)</td>
<td>26 (86.67%)</td>
<td>0.3¶</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>7 (10.14%)</td>
<td>2 (6.67%)</td>
<td></td>
</tr>
<tr>
<td>Cord</td>
<td>1 (1.45%)</td>
<td>2 (6.67%)</td>
<td></td>
</tr>
<tr>
<td>Donor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibling</td>
<td>32 (46%)</td>
<td>16 (53%)</td>
<td>0.2¶</td>
</tr>
<tr>
<td>MUD</td>
<td>35 (51%)</td>
<td>11 (37%)</td>
<td></td>
</tr>
<tr>
<td>Cord</td>
<td>1 (1%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Cousin</td>
<td>—</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>1 (1%)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

*P-values are for comparisons between cGVHD and no cGVHD. Statistically significant P-value (≤0.05). All statistical tests were performed using IBM SPSS (Statistical Product and Service Solutions) Version 19. †P-value was calculated by means of Mann-Whitney test. ‡P-value was calculated by means of Fisher’s Exact Test. §P-value was calculated by means of Cox-regression analysis. ¶P-value was calculated by means of Chi-squared test. HSCT, haemopoietic stem cell transplantation; MUD, matched unrelated donor; RIC, reduced intensity conditioning.
biochemistry. Eleven had received total body irradiation and eight were on prolonged courses of cyclosporine for cGVHD. Other factors that may contribute to renal impairment were hypertension ($n = 12$), steroid induced diabetes ($n = 2$) and conditions predating allo-HSCT (one hepatitis B virus-related membranous glomerulonephritis, one focal segmental glomerulosclerosis).

**Nervous system**

Five patients had peripheral neuropathy; pain was the commonest symptom. Three patients reported cognitive changes: decreased concentration, amotivation and forgetfulness. One patient suffered a cerebrovascular accident that was a terminal event. One patient experienced a transient ischaemic attack. One patient had progressive multifocal leukoencephalopathy secondary to tacrolimus.

**Ophthalmological**

Forty per cent ($40$ of $99$) reported eye symptoms: dryness, irritation and conjunctival injection. All were prescribed symptomatic treatment. Ophthalmic cGVHD was diagnosed in $20$ patients. Twenty per cent developed cataracts, $13$ of whom received total body irradiation developed cataracts.

**Respiratory tract**

Sixty-six per cent ($31$ of $48$) had normal lung function tests. Seventeen patients had bronchiolitis obliterans. An ex-smoker developed lung carcinoma after allo-HSCT.

**General health surveillance**

One patient reported to have a cracked tooth, and three had dental caries. The vaccination schedule was completed in $56$ patients. Fifteen patients had not been vaccinated, three of whom were deferred because of immunosuppression for cGVHD. Twenty-eight patients’ vaccination status was unknown. Papanicolaou (Pap) smears were up to date in $29$ of $44$ women, and $33$ were up to date with mammography. Two patients had cervical intraepithelial neoplasia, and one patient had vaginal intraepithelial neoplasia. Twenty-three per cent ($10$ of $44$) of women had no records of mammography or Pap smears.

**Malignancy after HSCT**

Fourteen patients developed skin cancers, including three with malignant melanoma. Three patients

---

**Table 3** Clinical manifestations of cGVHD ($n = 69$)

<table>
<thead>
<tr>
<th>Number of organs involved</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33 (48%)</td>
</tr>
<tr>
<td>2</td>
<td>23 (33%)</td>
</tr>
<tr>
<td>3</td>
<td>9 (13%)</td>
</tr>
<tr>
<td>4</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>5</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

**Musculoskeletal**
- Cramps
- Stiffness
- Arthralgia

**Integument**
- Sclerotic, morphea-like skin
- Nail dystrophy
- Scalp alopecia
- Hair thinning

**Ophthalmic**
- Xerophthalmia

**Eye pain**

**Oral cavity**
- Xerostomia
- Lichenoid changes
- Non-infectious ulceration
- Hyperkeratotic plaques
- Pain
- Mucositis/gingivitis/sialitis
- Mucosal atrophy

**Hepatic**

**Genitalia**
- Cervical/vaginal stenosis
- Scars
- Lichenoid changes

**Lung – obstructive changes**

**Gastrointestinal tract**
- Strictures
- Oesophageal webs
- Non-infectious diarrhoea
- Anorexia

**cGVHD manifestations**

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 (41%)</td>
</tr>
</tbody>
</table>

**Table 4** cGVHD severity and treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of study patients ($n = 99$) on treatment for cGVHD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not severe, no treatment needed</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>Treatment required</td>
<td>48 (48%)</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>44 (44%)</td>
</tr>
<tr>
<td>1 medication</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>corticosteroid monotherapy</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>2 medications</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>3 medications</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Psoralen Ultra-Violet A (PUVA)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>No longer on treatment</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

**Bone marrow transplant survivorship**

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developed solid organ malignancies 3–6 years after allo-HSCT: squamous cell lung carcinoma, transitional cell carcinoma and malignant fibrous histiocytoma.

**Late psychosocial effects of HSCT**

Please refer to Table 6 and 7.

**Return to vocation**

Social reintegration is an indicator of positive psycho-emotional well-being and includes resumption of activities of daily living including work or study. Thirty-eight per cent resumed their pre-transplantation vocation at full capacity: paid employment (n = 33), domestic duties (n = 2), study (n = 2) and volunteer (1). Sixteen per cent (16 of 99) resumed work at reduced capacity. Five per cent (5 of 99) retired. Seven per cent (7 of 99) were unable to return to work.

**QOL**

Twenty-seven patients (29%) were assessed by transplant haematologist to have problems, such as lethargy, depression, anxiety, unemployment, insomnia and pain.

---

**Table 5** Late physiological effects of HSCT: a comparison of SVH cohort and the Bone Marrow Transplant Survivor Study10 (BMTSS) data

<table>
<thead>
<tr>
<th>Late effects</th>
<th>SVH (n = 99) percentage of study population</th>
<th>BMTSS (n = 1022) percentage of study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>cGVHD requiring treatment</td>
<td>48%</td>
<td>29.8%</td>
</tr>
<tr>
<td>Life-threatening cardiovascular conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>2%</td>
<td>1.4%</td>
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<tr>
<td>Aortic dissection</td>
<td>1%</td>
<td>—</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Endocrine conditions requiring treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Zero</td>
<td>1.9%</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>24%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Infertility/ovarian failure</td>
<td>3%</td>
<td>NA</td>
</tr>
<tr>
<td>Reduced BMD, minimal trauma fractures</td>
<td>15%</td>
<td>NA</td>
</tr>
<tr>
<td>Severe gastrointestinal/hepatobiliary disease</td>
<td>1%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Life-threatening and severe infections</td>
<td>4%</td>
<td>NA</td>
</tr>
<tr>
<td>Recurrent infections affecting quality of life</td>
<td>3%</td>
<td>NA</td>
</tr>
<tr>
<td>Chronic kidney disease requiring renal replacement therapy</td>
<td>0%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Cataracts</td>
<td>20%</td>
<td>NA</td>
</tr>
<tr>
<td>Solid organ malignancy</td>
<td>3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Skin malignancy</td>
<td>14%</td>
<td>NA</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; cGVHD, chronic graft versus host disease; HSCT, haemopoietic stem cell transplantation; NA, not available; SVH, St Vincent’s Hospital.

---

**Table 6** Late psychosocial effects of HSCT: comparison of SVH cohort and BMTSS data11

<table>
<thead>
<tr>
<th>Psychosocial effect</th>
<th>SVH patients† (%)</th>
<th>BMTSS patients (n = 1065) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological distress, QOL issues</td>
<td>42/69 (61)</td>
<td>78.2</td>
</tr>
<tr>
<td>No psychological distress or QOL issues</td>
<td>27/69 (39)</td>
<td>21.8</td>
</tr>
<tr>
<td>Depression, severe or requiring treatment</td>
<td>7/99 (7)</td>
<td>11</td>
</tr>
</tbody>
</table>

†Incomplete data. BMTSS, Bone Marrow Transplant Survivor Study; HSCT, haemopoietic stem cell transplantation; QOL, quality of life; SVH, St Vincent’s Hospital.

---

**Table 7** Return to work after HSCT: comparison of SVH cohort with a Seattle study12

<table>
<thead>
<tr>
<th>SVH patients† (%)</th>
<th>Syrjala et al. (n = 319) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to vocation</td>
<td>54/66 (82)</td>
</tr>
<tr>
<td>Reduced capacity</td>
<td>16/66 (24)</td>
</tr>
<tr>
<td>Full capacity</td>
<td>38/66 (58)</td>
</tr>
<tr>
<td>Unable to work/retired after HSCT</td>
<td>12/66 (18)</td>
</tr>
</tbody>
</table>

†Incomplete data. HSCT, haemopoietic stem cell transplantation; SVH, St Vincent’s Hospital.

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Seven patients required anti-depressants. Forty-two patients were assessed to have no QOL issues during clinical reviews.

Patients’ self-assessment of QOL as measured by the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) version 4 questionnaire found that the average score is 85.8% (n = 62, 17 of whom were included in this study), which is comparable with the FACT-General Population score of 85.9% for a general Australian population.

Discussion

Data regarding long-term HSCT survivorship in Australia are scarce. To improve the care of allo-HSCT survivors, we undertook this retrospective study in light of recent overseas publications.10,11,14,15

Our study showed that the burden of chronic health conditions is high in allo-HSCT survivors. Ninety-one per cent of our population reported chronic physical health conditions, which is higher than the prevalence of 66% in the Bone Marrow Transplant Survivor Study (BMTSS).9 In the BMTSS (n = 1065, 469 autologous, 596 allogeneic), severe (grade 3 and 4) cGVHD, female sex, follow up ≥5 years from allo-HSCT (BMTSS median follow up 7.3 years, range 2–28 years), higher education and having health insurance were factors associated with increased chronic health conditions. Methodological differences and inclusion of autologous transplant patients in the BMTSS probably resulted in their lower burden of chronic health conditions. Our results are comparable with large allo-HSCT studies; less than half of long-term allo-HSCT survivors report normal functional status, QOL issues persist over time, and about 5% of very long-term survivors (>10 years) report their health as poor.16 A prospective study has shown that recovery is a process requiring 3–5 years.6

The incidence of cGVHD was 70% (69 of 99); 48% (48 of 99) of study patients required treatment for cGVHD which is at the lower end of published ranges for cGVHD (40–70%).7 A quarter of our study population had cardiovascular health problems, compared with 17% in the Australian population (age 16–85).17 Life-threatening CVS events in our study were cerebrovascular events (2%), coronary artery disease (2%), aortic dissection (1%) and cardiomyopathy (1%). Twelve per cent of our study population required treatment for dyslipidaemia. There may be an association between cGVHD and arterial disease.18 Other allo-HSCT-related cardiovascular complications are cardiomyopathies, arrhythmias and valvular dysfunction. Radiation therapy and anthracyclines are further cardiotoxins.19 The risk for metabolic syndrome in allo-HSCT survivors is cumulative20 and relates to cytokine-mediated inflammation.21 Malignancy survivors are more likely to be overweight, hyperglycaemic, have insulin resistance and lower high-density lipoprotein levels.22 Long-term allo-HSCT survivors have worse cardiovascular outcomes and increased prevalence of type 2 diabetes mellitus in longitudinal studies of paediatric transplant patients.23,24 Management foci should be preventative through education and control of modifiable risk factors, particularly obesity, tobacco, hypertension and dyslipidaemia. Each individual needs to have, at a minimum, screening suggested by the Heart Foundation.25

Loss of BMD affected one-third of our allo-HSCT patients. Corticosteroid and calcineurin inhibition exposure, cGVHD, hypogonadism, renal disease with secondary hyperparathyroidism, immobility, vitamin D and calcium deficiency were identifiable risk factors that should be minimised if possible.26 We endorse the involvement of endocrinologists, regular BMD measurements to assess efficacy of, and compliance with preventive and therapeutic measures. The incidence of hypogonadism was underreported by male patients, and few men (3 of 55) received HRT. This study highlighted clinicians’ responsibility to discuss sexual health with all transplant patients. Treating hypogonadism would further improve musculoskeletal health and QOL.

Allo-HSCT patients have an increased incidence of chronic kidney disease (CKD).27 CKD was identified in a quarter of our patients, comparable with other allo-HSCT populations.28 Total body irradiation, calcineurin inhibitors and platinum-based chemotherapy are risk factors.6 We seek to reduce and delay progression of CKD through minimisation of nephrotoxins, screening serum and urinary biochemistries and blood pressure regularly, and aggressively treat hypertension.

Infections contribute to non-relapse morbidity and mortality. Infection risks in allo-HSCT survivors are cGVHD and chronic immunosuppression. Variable immune reconstitution due to age, donor and stem cell source, human leucocyte antigen compatibility, underlying disease and the conditioning regimen also modify the infective risk. One (1%) study patient died of sepsis. Three patients (3%) had herpes simplex virus or herpes zoster virus reactivation. Our results are low for long-term allo-HSCT survivors. Antibody response to vaccination after allo-HSCT is variable, and patients with active cGVHD require individualised assessments. The post-transplant vaccination schedule was complete in 55% of our patients. This needs to be improved along with adherence to prophylactic antimicrobials, minimising immunosuppression and treating hypogammaglobulinaemia.

Almost half of our patients reported ophthalmic symptoms, and almost a quarter had cataracts. Late
ophthalmic complications reduce QOL. In addition to endorsing allo-HSCT survivor guidelines, we seek and recommend ophthalmological involvement early.

Almost a quarter of our subjects had respiratory problems. Obstructive patterns in respiratory function tests (RFTs) are associated with cGVHD and contribute to non-relapse mortality.²⁹ Restrictive changes are less common. As lung dysfunction may be asymptomatic and insidious, we schedule periodic RFTs on all allo-HSCT survivors. We counsel all patients to avoid tobacco.

New solid organ malignancies occurred in three patients (3%). Incidences of secondary malignancies are cumulative in transplant survivors,³⁰ twice the rate expected in the general population at 10 years (2–6%), and thrice the rate by 15 years.³

QOL incorporates physical, emotional, social and existential domains, and can be described as an individual’s satisfaction with his or her well-being. It is multi-dimensional and allows comparisons to be made between normative and cross-illness populations.³¹,³² QOL becomes increasingly important over time in a transplant survivor.³³ A standardised assessment of QOL, such as the FACT-BMT, is necessary and instrumental to optimising patients’ QOL. Our clinicians thought a quarter of the patients had unsatisfying QOL during clinical reviews. Yet, our patients assessed their own QOL more favourably, with a FACT-BMT score that is similar to the general Australian population. This discrepancy is instructive; first, a standardised method to assess QOL is necessary, and second, our patients’ QOL score may be used to educate and encourage potential allo-HSCT patients.

This study was a single-centre experience, and the results may not be generalisable. Because of the nature of retrospective analysis, data were incomplete as we were unable to collect every parameter on all patients. An obvious drawback of the retrospective methodology was incomplete assessments of patients, but our subjects were unselected and represent ‘real world’ experience in a local context.

Our study demonstrated the importance of a standardised and comprehensive protocol in caring for allo-HSCT survivors. Our study showed that in allo-HSCT survivors, renal, bone health, ophthalmic, respiratory and malignant physiological effects were adversely increased. QOL seemed to be on par with the general Australian population. The allo-HSCT patient, his/her general practitioner and any other healthcare workers involved would benefit from ongoing engagement, education and support from the allo-HSCT team.

**Conclusion**

Allo-HSCT patients are living longer with potential complications that warrant lifelong surveillance and engagement with healthcare. We have identified prevention of avoidable complications and continual education of the allo-HSCT patient and all healthcare workers involved as areas that will improve outcomes for allo-HSCT survivors. Based on our findings, we support the practices of long-term follow-up assessments of patients recommended by the international allo-HSCT survivor guidelines³⁴ in Australian transplant centres.

**Acknowledgements**

Ian Nivison-Smith for his contribution to statistical advice and analysis. Medical, nursing and allied health staff of St Vincent’s Public Hospital for their help.

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**References**


Bone marrow transplant survivorship

The Australia and New Zealand Fontan Registry: description and initial results from the first population-based Fontan registry


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Key words
Fontan procedure, heart defect, congenital, registry, outcome assessment (healthcare), research design.

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Abstract

Background: The Fontan procedure is the final in a series of staged palliations for single-ventricle congenital heart disease, which encompasses rare and heterogeneous cardiac lesions. It represents an unusual and novel physiological state characterised by absence of a subpulmonary ventricle.

Aims: The population is growing steadily, prompting creation of this registry to study their epidemiology, demographic trends, treatment and outcomes.

Methods: This multicentre, binational, prospective and retrospective, web-based registry involving all congenital cardiac centres in the region has identified nearly all Fontan patients in Australia and New Zealand. Patients identified retrospectively were approached for recruitment. New recipients are automatically enrolled prospectively unless they choose to opt-out. Follow-up data are collected yearly.

Results: Baseline data were obtained in 1072 patients as at 1 January 2011. Ninety-nine patients died; 64 were lost to follow up. Forty-four per cent of patients lost were between 20 and 30 years of age. The size of the Fontan population is increasing steadily. Among 973 living patients, 541 (56%) gave consent for prospective collection of follow up. Between 1 January 2011 and 1 January 2013, an additional 47 subjects were enrolled prospectively. The current proportion of patients operated with hypoplastic left heart syndrome is currently 29% and is growing rapidly.

Conclusion: The population surviving after the Fontan procedure has been growing in recent decades, especially since survival with hypoplastic left heart syndrome has improved. The Australia and New Zealand Fontan Registry provides population-based data, and only large databases like this will give opportunities for understanding the population and performing prospective trials.

Introduction

The Fontan population is growing worldwide, and its demographics are changing. In its most simple form, the Fontan procedure constitutes a direct connection between the systemic veins and pulmonary arteries, with absence of a subpulmonary ventricle. Based on an assumption that a subpulmonary ventricle is not strictly...
necessary for a functioning circulation, the Fontan procedure was initially described in 1971 for the surgical palliation of tricuspid atresia with right ventricular hypoplasia. Indications have now broadened to include any congenital cardiac lesion not amenable to a biventricular repair. In addition to hypoplasia of either ventricle, anatomical contraindications to biventricular repair—such as a straddling atroventricular valve or non-committed ventricular septal defect—occasionally mandate single ventricle palliation. Gradual improvements in our understanding of this unique physiology over the last 40 years have driven modifications in surgical technique to preserve kinetic energy within the Fontan conduit. Abandonment of the ‘classical’ atriopulmonary connection, which universally experienced massive atrial dilatation, resulted in widespread adoption of newer techniques that exclude part or all of the atrium in the Fontan pathway (the lateral tunnel and extracardiac conduit respectively).

Improvements in early outcomes have driven an increase in the number of patients surviving into adulthood after this ‘palliative’ procedure. Contemporary successes with the Norwood procedure for hypoplastic left heart syndrome (HLHS) are resulting in more children with more complex conditions undergoing the Fontan procedure. While single-ventricle patients represent only 1–3% of the live-born congenital heart disease (CHD) population, single-ventricle palliation has become one of the most common types of heart surgery undertaken at centres treating CHD. Children undergoing single-ventricle management make up 22% of primary procedures and 51% of mortalities, and consume the greatest resources among children with CHD.1

Long-term survivors of the Fontan procedure are at risk of arrhythmia, thromboembolism, protein-losing enteropathy, plastic bronchitis, heart failure and transplantation, or death. Reports are emerging of long-term liver and renal impairment secondary to the Fontan physiological state.2,4 However, no population-based data exist to demonstrate the magnitude of the potential problems that are likely to arise as this population ages. Fontan patients are a heterogeneous group, and the procedure is performed in small numbers at individual centres, with an incidence of 10 per 100 000 live births, making recruitment for small numbers at individual centres, with an incidence of a heterogeneous group, and the procedure is performed in centres treating CHD. Children undergoing single-ventricle management make up 22% of primary procedures and 51% of mortalities, and consume the greatest resources among children with CHD.3

The registry aims to enrol all patients who have undergone a Fontan procedure in Australia and New Zealand. Potential study subjects were identified by the lead clinician at each site (Appendix 1) using existing local databases. Additional cases were recruited by sending a flier to all congenital cardiologists on the mailing list of the Cardiac Society of Australia and New Zealand. Human Ethics approval was obtained from all participating centres (Appendix 2).

Inclusion criteria
Potential subjects underwent their first Fontan procedure within Australia or New Zealand after its first description in 1971.8 Fontan procedure was strictly defined as an atriopulmonary connection, lateral tunnel modification or extracardiac conduit. Patients undergoing the Björk modification, in which a hypoplastic but functional subpulmonary ventricle was incorporated by means of a right atrium to right ventricle conduit, were excluded. There were no restrictions on the prosthetic materials used to construct the Fontan pathway. The present description includes patients whose Fontan procedure was performed between 1 January 1975 and 1 January 2013.

Baseline data collection
The registry has been designed to collect longitudinally a limited amount of data on a large proportion of patients. The data fields collected are specified in Table 1. All data from birth to the last date of follow up were collected during a series of site visits to participating centres and reviewed by a single investigator (AJI). Data consist of baseline and retrospective follow-up data. Retrospective follow-up data were obtained from the participating centres and by contacting private cardiologists directly.

Consent process and prospective follow up
After identification of the patient population, living patients were contacted initially by mail-out and then by a phone consent process. Prospectively, all patients...
undergoing the Fontan procedure are automatically enrolled to the registry unless they or their parent/guardian choose to opt-out. Once enrolled, participants consent to the yearly collection of follow-up correspondence and echocardiogram reports from their treating cardiologist. They are also asked if they wish to be contacted for future substudies. Participants not seen by a cardiologist within the past 2 years are contacted to prompt a follow-up visit.

In response to the limitations of written informed consent encountered by other registries, institutional approval was granted for automatic recruitment of deceased patients and patients lost to follow up to ensure recruitment of a representative sample of participants. Linkage to the National Death Index will occur 5-yearly to identify the fate of patients lost to follow up.

**Database**

Study data were collected and managed using REDCap electronic data capture tools hosted at the Murdoch Children’s Research Institute. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: (i) an intuitive interface for validated data entry; (ii) audit trails for tracking data manipulation and export procedures; (iii) automated export procedures for seamless data downloads to common statistical packages; and (iv) procedures for importing data from external sources.

**Governance**

All collaborations and access to data are overseen by the Fontan Registry Steering Committee (Appendix 1).

**Results**

**Loss to follow up and attrition from Fontan physiology**

After collection of baseline data, 1072 eligible patients operated on prior to 1 January 2011 were identified, of whom 99 (8%) were deceased (36 perioperative hospital deaths, 63 late deaths). Among 973 living patients, 754 (77%) had follow up within 2 years of the time of data collection at each of the centres. No follow-up information was available in 64 patients (7%) who were completely lost to follow up. Seventeen patients (2%) were living after transplantation or Fontan takedown to an intermediate palliation such as a bidirectional cavopulmonary (Glenn) shunt or systemic-to-pulmonary shunt (14 and 3 patients respectively). Twenty-two patients (2%) have entered their fifth decade of life.

**Recruitment**

Consent for collection of yearly follow up was sought from living patients operated prior to 1 January 2011, who were not taken down or transplanted. Figure 1
summarises the recruitment and consent process. Out of 956 eligible subjects, 64 (7%) were lost to follow up and could not be contacted, 543 (57%) gave consent, 4 refused (0.4%) and 345 (36%) did not respond. A phone consent process is currently under way to improve recruitment of non-responders, and to date has a success rate of 97% (two refusals from 63 approached).

A further 47 subjects operated since 1 January 2011 have been enrolled automatically. The pool of consented subjects not transplanted or taken down number 590 as of 1 January 2013. The demographics of enrolled versus non-enrolled subjects are outlined in Table 2. Enrolled subjects tended to be more closely followed up and younger.

**Population growth and morphological distribution**

Figure 2 illustrates the growth in the size of the Fontan population and a rapid recent growth in the proportion with hypoplastic left heart syndrome (HLHS). The peak incidence of the Fontan procedure in Australia and New Zealand was 63 per year, in 2006. Based on 2006 census data, the combined population of the two nations was...
The peak proportion of patients with a diagnosis of HLHS was 29% (17/59 pts) in 2009. The number in each morphological subgroup is given in Table 3. Left ventricular morphological dominance is present in 60% of the cohort (643/1072 pts).

### Discussion

We report the design and creation of the first population-based registry of patients who have undergone a Fontan procedure. This binational multicentric registry is unique in its combined retrospective and prospective design. The registry has four aims:

1. **To facilitate understanding of the changing composition and health outcomes of this cohort through population-based, longitudinal follow up**

   Unlike other cohort studies of Fontan patients, such as the North American Pediatric Heart Network Fontan Study and the European multicentric Fontan study, this is the first description of an entire population of Fontan patients. Hence, it does not suffer from referral bias. The care and the make-up of this group of patients are representative of most Fontan patients in similar healthcare systems present in Europe. This is evidenced by the higher proportion of right ventricular dominance and HLHS present in the other cohorts compared with this one.

   In the creation of this registry, we have demonstrated growth in the population, the rate of Fontan completion and the proportion with HLHS. The improved results in the neonatal treatment of patients with HLHS has led to patients with this diagnosis becoming one the most common subgroups being successfully treated through to Fontan completion. These patients require more extensive operations and develop more short- and long-term complications and reinterventions.

   The earliest recipients of the Fontan procedure are now entering their fifth decade of life and are increasingly at risk of the late complications of atrial dilatation, thromboembolism, atrial arrhythmias and venous hypertension. The Fontan registry will provide data on the rates of these outcomes.

2. **To better delineate associations between long-term outcomes and modifiable factors such as surgical procedural modifications and postoperative medical treatments**

   Little evidence exists to inform clinicians of the best medical and surgical options for Fontan patients. The ideal age at which to complete the Fontan circulation remains controversial, as does the long-term benefit of pathway fenestration. Medications, including anticoagulants and antihypertensives, may be offered and continued for variable periods of time. Some patients are advised to refrain from strenuous physical activity; however, there is an emerging body of evidence that aerobic training may improve quality of life and survival. Fontan patients currently receive widely disparate advice about the safety of pregnancy, and the safety of contraception in this group, who are already at increased risk of thromboembolism, is not known. Substudies are currently under way on this dataset to analyse the effect of these modifiable risk factors on long-term outcomes.

3. **To provide important information for health service provision and planning**

   The proportion of the Fontan population who ultimately ‘fail’ and require heart transplantation is unknown. In the coming years, longitudinal follow up obtained through this registry will enable clear risk stratification for rates of mortality, reoperation and arrhythmia. Perhaps most importantly, estimation of the looming cardiac transplant demand will not only assist infrastructure development and prioritisation but also patient and family expectations given the small pool of donor organs in Australia and New Zealand.

   Long-term follow up of patients after completion of the Fontan operation is crucial to enable proactive interventions aimed at prevention prior to the onset of serious complications.

### Table 3 Morphological diagnoses of patients operated on before 1 January 2011

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Consented $(n = 543)$</th>
<th>Non-consented $(n = 413)$</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA</td>
<td>121 (22%)</td>
<td>108 (26%)</td>
<td>229 (24%)</td>
</tr>
<tr>
<td>HLHS</td>
<td>54 (10%)</td>
<td>30 (7%)</td>
<td>84 (9%)</td>
</tr>
<tr>
<td>DORV</td>
<td>66 (12%)</td>
<td>71 (17%)</td>
<td>137 (14%)</td>
</tr>
<tr>
<td>AVSD</td>
<td>41 (8%)</td>
<td>19 (5%)</td>
<td>60 (6%)</td>
</tr>
<tr>
<td>AVSD-DORV</td>
<td>21 (4%)</td>
<td>17 (4%)</td>
<td>38 (4%)</td>
</tr>
<tr>
<td>TGA</td>
<td>25 (5%)</td>
<td>22 (5%)</td>
<td>47 (5%)</td>
</tr>
<tr>
<td>ccTGA</td>
<td>31 (6%)</td>
<td>15 (4%)</td>
<td>46 (5%)</td>
</tr>
<tr>
<td>DILV</td>
<td>98 (18%)</td>
<td>80 (19%)</td>
<td>178 (19%)</td>
</tr>
<tr>
<td>PA-IVS</td>
<td>42 (8%)</td>
<td>34 (8%)</td>
<td>76 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>44 (8%)</td>
<td>17 (4%)</td>
<td>61 (6%)</td>
</tr>
</tbody>
</table>

AVSD, atrioventricular septal defect; ccTGA, congenitally corrected transposition of the great arteries; DILV, double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; PA-IVS, pulmonary atresia with intact ventricular septum; TA, tricuspid atresia TGA, transposition of the great arteries.
complications. The majority of cardiologists accordingly aim to review their patients annually while they are asymptomatic. In reality, other series have demonstrated 30–50% will eventually become lost to follow up.18,19 Re-presentation for care after a lapse in follow up is often late after the onset of symptoms, when simple interventions are likely to be unsuccessful. In Australia and New Zealand, we have shown the rate of loss to follow up to be much lower and the rate of concurrency of follow up to be reassuringly high. However, there are improvements still to be made, and the process of creating and maintaining the registry will promote a focus on follow up among patients and clinicians.

4 To enable recruitment for prospective, randomised trials

The number of patients at single centres who are unwell enough to be eligible for trials of medical therapies such as pulmonary vasodilators is small, making multicentric recruitment essential. On the flip side, very large samples are required to demonstrate the efficacy of medical therapies with small effects in Fontan patients, for example angiotensin-converting enzyme inhibitors. Currently only seven randomised, controlled trials exist in Fontan patients.20–26 The two largest were arguably underpowered and/or of insufficient duration to demonstrate a treatment effect.21,23 Creation of the registry has identified a large enough pool of eligible subjects to enable recruitment for large-scale prospective and cross-sectional studies in Australia and New Zealand.

Limitations

The Fontan population is a disparate population with a spectrum of conditions and prior palliations. Thus, each subgroup may differ significantly in its characteristics and outcomes; however, the creation of the registry enables sufficient numbers for these differences to be detected with reasonable statistical power.

A small number of patients have undergone a Fontan procedure overseas and now migrated to Australia or New Zealand. These patients have not been included in this initial description; however, they are enrolled in the registry, and their clinical data have been collected. On recruitment to the registry, the participants do not undergo a panel of investigations. The initial results of the cohort are based on retrospective medical history information, with the inherent limitations of retrospective cohort studies.

Beyond yearly survival, the health information of participants is obtained from the letter and echocardiogram of the treating cardiologists. While this is a small group of physicians with extensive subspecialty training and similar clinical approaches, some variation in the subjective grading of patients’ clinical condition is inevitable.

Conclusion

The Australia and New Zealand Fontan Registry provides population-based data, and only large databases like this will give opportunities for understanding the population and performing prospective trials.

Acknowledgements

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References

Appendix 1

Paediatric and adult congenital cardiac centres collaborating in the Australia and New Zealand Fontan Registry.

Australia:
The Royal Children’s Hospital and Murdoch Children’s Research Institute, Melbourne, Victoria
The Royal Melbourne Hospital, Melbourne, Victoria
Monash Medical Centre, Melbourne, Victoria
The Children’s Hospital at Westmead, Sydney, New South Wales
The Royal Prince Alfred Hospital, Sydney, New South Wales
The Women’s and Children’s Hospital, Adelaide, South Australia
Royal Adelaide Hospital, Adelaide, South Australia
Mater Children’s Hospital, Brisbane, Queensland
Prince Charles Hospital, Brisbane, Queensland
Princess Margaret Hospital, Perth, Western Australia
The Royal Perth Hospital, Perth, Western Australia

New Zealand:
The Starship Children’s Hospital, Auckland

Appendix 2

Key members of the Australia and New Zealand Fontan Registry Steering Committee.

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Hospital</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Professor Yves d'Udekem</td>
<td>Paediatric Cardiac Surgeon</td>
<td>Royal Children's Hospital</td>
<td>Melbourne, Australia</td>
</tr>
<tr>
<td>Associate Professor Tom Gentles</td>
<td>Paediatric Cardiologist</td>
<td>Starship Children's Hospital</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Associate Professor David Winlaw</td>
<td>Paediatric Cardiologist</td>
<td>Westmead Children's Hospital</td>
<td>Sydney, Australia</td>
</tr>
<tr>
<td>Associate Professor Robert Weintraub</td>
<td>Paediatric Cardiologist</td>
<td>Royal Children's Hospital</td>
<td>Melbourne, Australia</td>
</tr>
<tr>
<td>Dr Sarah Hope</td>
<td>Paediatric Cardiologist</td>
<td>Monash Medical Centre</td>
<td>Melbourne, Australia</td>
</tr>
<tr>
<td>Dr Gavin Wheaton</td>
<td>Paediatric Cardiologist</td>
<td>Women’s and Children’s Hospital</td>
<td>Adelaide, Australia</td>
</tr>
<tr>
<td>Dr Andrew Bullock</td>
<td>Paediatric Cardiologist</td>
<td>Princess Margaret Hospital</td>
<td>Perth, Australia</td>
</tr>
<tr>
<td>Dr Robert Justo</td>
<td>Paediatric Cardiologist</td>
<td>Mater Children’s Hospital</td>
<td>Brisbane, Australia</td>
</tr>
<tr>
<td>Dr Leeanne Grigg</td>
<td>Adult Congenital Cardiologist</td>
<td>Royal Melbourne Hospital</td>
<td>Melbourne, Australia</td>
</tr>
<tr>
<td>Professor David Celermajer</td>
<td>Adult Congenital Cardiologist</td>
<td>Royal Prince Alfred Hospital</td>
<td>Sydney, Australia</td>
</tr>
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<td>Adult Congenital Cardiologist</td>
<td>Adult Congenital Cardiologist</td>
<td>Prince Charles Hospital</td>
<td>Sydney, Australia</td>
</tr>
<tr>
<td>Dr Dorothy Radford</td>
<td>Adult Congenital Cardiologist</td>
<td>Princess Margaret Hospital</td>
<td>Brisbane, Australia</td>
</tr>
<tr>
<td>Ms Victoria Forsdick</td>
<td>Fontan Recipient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mrs Rachel Bishop</td>
<td>Parent of Fontan Recipient</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Impact of a compulsory final year medical student curriculum on junior doctor prescribing

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Key words
prescribing, medical education, medication safety.

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Abstract

Background: Attendance at face-to-face sessions and completion of online components of the National Prescribing Curriculum was made compulsory for final year medical students at the University of Adelaide in 2010.

Aims: To determine the impact of a compulsory prescribing curriculum for final year medical students on their prescribing competencies at the start of clinical practice. Graduates’ attitudes to their medical school training in prescribing were also surveyed.

Methods: Two cohorts of medical graduates from the University of Adelaide who commenced medical practice in 2010 and 2011 were required to complete a prescribing task using the National Inpatient Medication Chart (NIMC) at orientation and after 6 months of clinical practice. The main outcome measure was a performance in a scenario-based prescribing test, as determined by test scores and overall safety of prescriptions at orientation and 6 months of clinical practice.

Results: There was a small difference in the average total score for the prescribing task between the 2010 and 2011 cohorts at orientation (P = 0.0007). The 2011 cohort had a higher number of safer charts at commencement of practice. We found no difference between the 2010 and 2011 cohorts in attitudes towards their undergraduate pharmacology education, and new graduates feel poorly prepared.

Conclusion: Medical graduates who are required to complete a practically oriented prescribing curriculum in final year perform slightly better on a prescribing assessment at commencement of practice. More work on preparing graduates for this complex task before graduation is needed.

Introduction

Deficiencies in the ability of junior doctors to prescribe safely and adequately for hospital inpatients have been highlighted in the medical literature. 1,2 Prescribing medications is a critical part of medical practice and begins from the first day of practice. While many of the prescribing errors are attributed to the work environment and junior doctor workload, some authors have highlighted the inability of medical curricula to prepare junior doctors for this task. 3–5 Junior doctors themselves cite deficiencies in their training as a contributor to their inadequate prescribing skills. 5,6

The National Prescribing Curriculum (NPC) (http://www.nps.org.au/npc) was developed by NPS MedicineWise (formerly known as the National Prescribing Service) in collaboration with the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists and was made available to all Australian medical schools in 2001. 7 The University of Adelaide Medical School utilises the NPC in the final year of a 6-year undergraduate medical curriculum. The University of Adelaide programme consists of 10 face-to-face tutorials with a clinical pharmacologist to complement the online modules. Following completion of each module, a face-to-face tutorial session is held where the students can ask questions to clarify and further expand on the work they have completed online. These prescribing sessions integrate well with previous elements of the University of Adelaide medical school curriculum, which provide basic clinical pharmacological and pharmacotherapy concepts. Previously, the uptake of the prescribing curriculum at the University of Adelaide was very poor, with attendance as low as 25% in some sessions. To enhance the prescribing skills of all medical graduates, the sixth year prescribing curriculum was made a compulsory element for final year students from January 2010.
As a large proportion of University of Adelaide graduates choose to undertake their internship at the Royal Adelaide Hospital (RAH), the transition of the prescribing curriculum from optional to compulsory offered a unique opportunity to evaluate the impact of completing the course in the prescribing competencies of new graduates.

Methods

Study design

This study aimed to evaluate new graduates’ competency in prescribing and to compare the effect of completing a compulsory prescribing curriculum. All interns commencing duty at the Royal Adelaide Hospital in January 2010 and 2011 were given a prescribing task during their orientation programme. A survey was also conducted to obtain the graduates’ views on the undergraduate prescribing curriculum. In January 2010, final year medical students at the University of Adelaide were required to complete the NPC online modules and attend at least 95% of the face-to-face tutorials. Failure to complete the programme was a barrier to graduation; these students formed the 2011 cohort. Interns who were graduates of the University of Adelaide thus formed a control (2010 cohort) and intervention (2011 cohort) group for comparison. Although we were only targeting University of Adelaide graduates, all interns were included in the survey to simplify the study process (this was easier than selecting a group). Analysis was then limited to the target group. Ethics approval was obtained from the Royal Adelaide Hospital Ethics Committee, and written consent was obtained from all participants before their inclusion in the study.

The task was performed prior to any orientation by the pharmacy or pharmacology departments, and was the same case scenario utilised by Hilmer et al. in their study of new graduates at NSW hospitals in 2008. The task was modified slightly from Hilmer’s study (to exclude the discharge prescription component). This was necessary due to changes in the local hospital process for discharge scripts. Study participants were required to write a prescription for the patient on the Australian National Inpatient Medication Chart (NIMC). All graduates were supplied with the necessary drug information for the prescribing tasks including the approved product information for each drug related to the case from local resources including Monthly Index of Medical Specialties and Australian Medicines Handbook monograph, in addition to prescribing guidelines for neutropenic fever from Therapeutic Guidelines and a copy of the NIMC.

Following 6 months of medical practice, interns were reassessed with the same prescribing task.

Prescriptions were scored independently by two clinical pharmacologists (JT and SS) according to pre-specified criteria. Discrepancies were reconciled by consensus. One point was awarded for each of the following parameters (total possible marks = 36):

- At least two unique patient identifiers recorded (e.g. name and date of birth)
- Complete allergies recording
- Regular medications charted (for each medication) – one point for each of: date, route, generic name, dose/frequency, signature/name of prescriber
- Slow release box ticked for sustained-release morphine (MS Contin)
- Paracetamol charted (as needed or regular) – one point for each of: date, generic name, route, dose/frequency, signature/name of prescriber
- Ticarcillin with clavulanic acid (Timentin; GlaxoSmithKline, Aspen Pharmacare Australia Pty Limited, Sydney, NSW, Australia) – not charted due to documented penicillin allergy
- Gentamicin – not charted (in preference for cefepime as per supplied guidelines)
- Additional ‘as needed’ analgesia charted – one point each for: opioid, immediate release, oral route, appropriate dose (equivalent 10–15 mg oral morphine), frequency 2–4 hourly, legal opioid order

To add a more realistic measure of competence, charts were also classified as ‘safe, moderately unsafe or severely unsafe’ by JT and SS according to potential to cause harm, based on a standardised method. All interns were given general feedback about prescribing performance at the end of orientation; in addition they were offered the option to receive individual feedback on their performance by email.

Statistical analysis

Each parameter was given one mark for correct completion, and the total task score was a count of parameters completed correctly. The changes in the average total score from orientation to 6 months in the two cohorts were compared by using a marginal log-linear model using generalised estimating equations (GEE) with a Poisson distribution and a log link function. GEE proportional odds regression, with a multinomial distribution and a cumulative logit link function was used to estimate the odds of the graduates writing safer prescription over the 6-month duration for both cohorts.

Graduates’ attitude towards their undergraduate pharmacology education was also compared between the two cohorts. The responses were aggregated to three groups of ‘strongly disagree/disagree’, ‘neutral’ and ‘strongly agree/agree’. Fisher’s exact test was used to assess the
association between the two cohorts and graduates’ attitude.

Results were considered statistically significant if \( P \)-value < 0.05. The analyses were carried out with the use of statistical analysis software SAS version 9.13 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 153 interns completed the task. Analysis was limited to graduates from the University of Adelaide, which constituted 68% (\( n = 50 \)) of the 2010 cohort and 75% (\( n = 59 \)) of the 2011 cohort commencing work at RAH. Response rate for the survey was 100%. Females comprised 60% of the 2010 cohort and 57.6% of the 2011 cohort. Mean age was 23.7 (± SD 0.886) years for 2010 cohort and 24.8 years (± SD 3.85) for 2011.

There was a significant difference in the average total score between the 2010 cohort (28.64 ± SD 3.2) and 2011 cohort (30.63 ± SD 2.8) at orientation (\( P = 0.0007 \)) and no difference (\( P = 0.6125 \)) between the cohorts after 6 months of medical practice (2010 cohort, 30.6 ± SD 2.5; 2011 cohort, 30.36 ± SD 3.0). The control cohort improved their average total score significantly after 6 months of medical practice (\( P = 0.0004 \)), while the intervention cohort remained statistically unchanged (\( P = 0.5532 \)).

The safety level of charts at orientation and after a 6-month period for both cohorts is summarised in Table 1. Overall, at orientation, the intervention cohort completed a higher rate of safe charts than the control cohort. Most charts rated as ‘severely unsafe’ for both cohorts were due to the charting of penicillin-based antibiotic (in the context of a documented penicillin allergy). The proportion of ‘severely unsafe’ charts due to charting penicillin was: 2010 cohort baseline 82.6%, 6 months 75.0%; 2011 cohort baseline 95.5%, 6 months 75.0%. Other reasons for ‘severely unsafe’ charts included inappropriate high opioid doses and inappropriate antibiotic doses (e.g. three times daily gentamicin). The most common reason for ‘moderately unsafe’ charts was failure to tick the slow release designation box for modified release opioids. Other reasons for ‘moderately unsafe’ charts included inadequate antibiotic cover, high opioid doses, omitted or inappropriate opioid frequency and duplicate paracetamol orders (on regular and prn charts). The odds of completing a safer chart after 6 months of clinical experience increased significantly from orientation for both cohorts (2010 cohort, GEE, \( P = 0.002 \); 2011 cohort, GEE, \( P < 0.001 \)) (Table 2).

Despite the intervention (compulsory NPC module completion and attendance at tutorials) and the difference in performance, we found no difference between the two cohorts in the graduates’ attitudes towards their undergraduate pharmacology education (Fig. 1). In the survey, less than half of the graduates indicated that they felt adequately trained to prescribe medications, and the majority indicated they would like to have more training in pharmacology in the undergraduate curriculum.

<table>
<thead>
<tr>
<th>Level of safety</th>
<th>2010 cohort (( n = 50 ))</th>
<th>2011 cohort (( n = 59 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Orientation 6 months</td>
<td>Orientation 6 months</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Safe</td>
<td>13 (26.0)</td>
<td>25 (50.0)</td>
</tr>
<tr>
<td>Moderately unsafe</td>
<td>14 (28.0)</td>
<td>17 (34.0)</td>
</tr>
<tr>
<td>Severely unsafe</td>
<td>23 (46.0)</td>
<td>8 (16.0)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of safety</th>
<th>2011 cohort (( n = 59 ))</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Orientation 6 months</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
</tr>
<tr>
<td>Safe</td>
<td>22 (37.3)</td>
</tr>
<tr>
<td>Moderately unsafe</td>
<td>15 (25.4)</td>
</tr>
<tr>
<td>Severely unsafe</td>
<td>22 (37.3)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Total scores</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At orientation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011 cohort vs 2010 cohort</td>
<td>1.59</td>
<td>0.77–3.29</td>
<td>0.21</td>
</tr>
<tr>
<td>2010 cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months vs orientation</td>
<td>3.40</td>
<td>1.54–7.51</td>
<td>0.002</td>
</tr>
<tr>
<td>2011 cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months vs orientation</td>
<td>4.13</td>
<td>2.01–8.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>After 6 months practice</td>
<td>1.94</td>
<td>0.94–3.99</td>
<td>0.073</td>
</tr>
<tr>
<td>2011 cohort vs 2010 cohort</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 1. Level of safety of the prescriptions written by interns at orientation and 6 months of their internship

Table 2. The proportional odds of interns completing a safer chart

Figure 1. Survey results comparison between 2010 and 2011 cohorts, conducted at orientation. Question 1: I feel adequately trained to prescribe medications in my first year of practice. Question 2: I feel that my training in pharmacology was equivalent or better than medical training in other areas. Question 3. I feel that I have adequate understanding of common medications and their adverse effects. Question 4. I would have liked to have more training in pharmacology as a medical student. ■, strongly disagree/disagree; , neutral; ■■, strongly agree/agree.
Discussion

In this study, the NPC online prescribing course, supplemented with tutorials, had only a small effect on improving the prescribing performance and safety of new graduates. There are recent reports of e-learning improving prescribing knowledge; however, didactic prescribing education in itself may not improve prescribing skills. Ideally, we would hope that when case-based e-learning is blended with tutorials, the improved knowledge translates to clinical practice, and new graduates are better prepared to prescribe when they start medical practice. Blended e-learning approaches have been shown to be useful in other fields of medical practice such as clinical skills, dermatology and acute medicine. However, we have been unable to demonstrate a sizeable impact in this study. Prescribing is a complex skill and requires a multifaceted approach throughout undergraduate training and beyond. As with all skills, practice is an important means of improvement, and we believe there is added value in providing hands-on experience (during undergraduate training) to develop prescribing skills.

The improved score and safety of the prescriptions of the 2010 cohort after 6-month clinical experience suggests real-life practice during their first year of work in the hospital also has only a small effect on prescribing skills. The positive effect of clinical experience has been noted previously. One can surmise that there could be potential harm to patients due to poor prescribing skills in this initial period of clinical practice, and that this harm is avoidable if new graduates are adequately trained to prescribe. Similarly safety of prescribing was enhanced by effective training and further improved with clinical experience. This lends credence to greater practical exposure prior to commencing work. The current NPC programme at University of Adelaide runs in one semester of final year and does not utilise all modules. This limited exposure may explain the small effect.

The small effect size may also reflect the study’s limitations. Given that most of the graduates in our study for whom the prescribing training was optional had some level of exposure to the online modules, the full impact of completing the NPC online course and accompanying tutorial programme was probably underestimated by this study. The study was only performed at one site, although performance was similar to that obtained by Hilmer et al. in particular, the rate of charting a penicillin-based antibiotic by the control cohort in this study is similar. The case scenario used has limitations in that it does not test all types and elements of prescribing. Other limitations include the repetition of the same scenario at 6 months to evaluate skills. Potential recall of the scenario may have affected the results. However, utilising the same scenario has more benefits for direct comparison, and the multiple components of the task decreases the likelihood of recall bias. Perhaps a more valid measure of prescribing skills would be to examine the real outcomes of poor prescribing. However, this would be a far more resource-intensive study.

Additionally, the researchers were not blinded to which cohort the students belonged to, and whether the NIMC was completed at orientation or at 6 months of medical practice. However, this is unlikely to have biased the findings as a systematic approach was used to rate the safety and accuracy of prescriptions. The main limitation of our study is that it was performed at one hospital and one medical school, and therefore the results may not be generalised. Despite these potential limitations, our study provides crucial insight into the impact of prescribing education in junior doctors’ prescribing skills and how their skills evolve with clinical practice.

Although the NIMC was originally designed for completion of the ‘indication’ field to be compulsory, omission is culturally acceptable in many institutions. In many instances a junior doctor’s ability to ascertain this parameter for all medicines is not reasonable with current workflow and the resources available. The University of Adelaide teaching programme recognises this issue and deliberately chose not to emphasise completion of this field. Therefore, we did not award points for completion of the ‘indication’ field in the prescribing task. However, the value of documenting a medication’s indication should not be dismissed, as it remains critically important when assessing risks and benefits of some medications such as warfarin and prednisolone. Importantly, we believe doctors’ prescribing behaviour is heavily influenced by what happens in hospitals, therefore the efficacy of any initiative in undergraduate education would be enhanced by similar initiatives and consistent messages in the workplace. Furthermore, there may be benefit from appropriate feedback mechanisms between hospitals and universities when prescribing issues are identified.

Despite the difference in the volume of prescribing education received and performance on the prescribing task, graduates’ attitudes are very similar in both cohorts with most feeling inadequately prepared to prescribe. Similar results about undergraduate opinions on pharmacology training have been reported previously. Students’ concerns about their prescribing ability may seem justified given the high rate of unsafe charts, although there are potential pitfalls in relying solely on student perception in evaluating usefulness of curricula as opposed to measuring educational outcomes. The task and scoring system used is somewhat artificial, in particular there is no facility to question the consultant’s instruction to use penicillin. Building a safe workplace culture to
allow questioning of instructions must be seen as an important adjunct to any educational prescribing programme. Undergraduate teaching in safety and quality, in particular how to raise concerns within a team are vital elements of safe prescribing education.

The information gained from this study has enabled us to refine the University of Adelaide prescribing curriculum and include earlier introduction to, and more opportunities for students to practice prescribing. This now begins in third year with the introduction of prescribing scenarios, utilising the NIMC. We also seek to increase the number to NPC modules completed by students in final year. A similar approach across all medical schools, as described in World Health Organization’s Guide to Good Prescribing, would ensure all graduates are optimally prepared to commence work. Frequent opportunities to practice prescribing actively in a realistic setting during the course will better prepare all medical graduates to prescribe safely and consistently. Medical schools in Australia need to consider incorporating the NPC curriculum to allow practical experience with this modality.

Conclusions

Medical graduates who are required to complete a practically oriented prescribing curriculum in final year perform better on a prescribing assessment at the start of medical practice. However, the difference is small, and students feel underprepared for commencing work. Online e-learning resources supplemented with tutorials can enhance new graduates’ prescribing skills, but exposure must be sufficient to enhance skills and confidence. All prescribing curricula should contain a significant practical component to ensure skills are optimised prior to commencing work.

References


Thomas et al.
Quality of care factors associated with unplanned readmissions of older medical patients: a case–control study

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Key words
quality of care, unplanned readmission, older medical patient.

Abstract

Background: Unplanned readmissions befall up to 25% of acutely hospitalised older patients, and many may be potentially preventable.

Aim: To assess the type and prevalence of quality of care factors associated with potentially preventable readmissions to a tertiary hospital general medicine service.

Methods: A retrospective case–control study was undertaken of hospital records of patients 65 years or older admitted acutely between 1 January 2005 and 31 December 2010. Readmissions up to 30 days postdischarge (cases) were purposively sampled according to frequencies of primary discharge diagnoses coded during the study period. Non-readmitted patients (controls), matched according to age, sex and primary discharge diagnosis on index admission, were selected in a 1.7:1 ratio.

Results: One hundred and thirteen cases and 198 controls were analysed, the former demonstrating a significantly higher comorbidity burden (mean (± standard deviation) comorbidity score 6.6 (±2.2) vs 5.6 (±2.4), P = 0.003) and a higher proportion of individuals with one or more hospitalisations over the preceding 6 months (55.7% vs 8.1%, P < 0.001). Among readmitted patients, 50 (44.3%) were associated with one or more quality factors versus 23 (11.6%) controls (P < 0.001). The most common were: failure to develop/activate an advance care plan (18, 15.9% vs 2, 1.0%; P < 0.001); suboptimal management of presenting illness (13, 11.4% vs 0, 0%; P < 0.001); inadequate assessment of functional limitations (11, 9.7% vs 0, 0%; P < 0.001); and potentially preventable complication of therapy (8, 7.1% vs 1, 0.5%, P = 0.002).

Conclusions: Quality of care factors are more common among readmitted than among non-readmitted older patients suggesting potential for remedial strategies. Such strategies may still have limited effects as older, frail patients with advanced diseases and multimorbidity will likely retain a high propensity for readmission despite optimal care.

Introduction

Unplanned hospital readmissions are common and costly. Studies in the US show that between 15%1 and 20%2 of all patients discharged from hospital are readmitted within 30 days, of which 90% are unplanned and at least 80% relate to an acute medical complication.3 Readmission rates for older general medicine patients are even higher ranging between 17%4 and 25%.4 Patients most at risk of readmission include those 80 years or older, with five or more comorbidities, cognitive impairment, impaired functionality, advanced stage illness or multiple prior acute admissions.5–7

Many investigators argue factors beyond the control of hospital staff such as level of disability, socioeconomic disadvantage, health literacy barriers, and impaired access to high-quality primary care and social support account for many, if not most, unplanned readmissions.8–10 Others highlight potentially preventable problems with inpatient care and discharge processes that may predispose to readmission.11–15 These include inaccurate diagnostic work-up, undertreatment of presenting illnesses or comorbid diseases, inadequate functional needs assessment, premature discharge, poor information transfer to community clinicians, omission of advanced care planning or palliative care, and failure to arrange follow-up review or community support. A recent systematic review of 34 studies that assessed the frequency of readmissions deemed potentially
predicting individual risk of readmission,20 including interventions remains problematic as decision rules for non-readmitted controls. Non-readmitted patients by analysing and comparing studies, we assessed whether such factors were unique to tertiary hospital general medicine service. We also aimed missions among a cohort of older patients admitted to a quality of care factors associated with unplanned readmission rates are now, rightly or wrongly, attracting attention as quality indicators,13 with consideration of financial penalties if hospital-specific, risk-adjusted readmission rates exceed peer-referenced benchmarks.15 Moreover, recent studies have revealed peridischarge strategies that can help reduce unplanned readmissions significantly.15–19 However, targeting these interventions remains problematic as decision rules for predicting individual risk of readmission,20 including potentially avoidable readmission,21 are inaccurate and of limited utility. At a system of care level, geographical locales, hospital setting and organisational factors associated with potentially preventable readmissions also remain ill-defined.22

We sought to determine the nature and prevalence of quality of care factors associated with unplanned readmissions among a cohort of older patients admitted to a tertiary hospital general medicine service. We also aimed to identify patient characteristics associated with quality factors. In overcoming a limitation of most previous studies, we assessed whether such factors were unique to readmitted patients or common to both readmitted and non-readmitted patients by analysing and comparing care of readmitted cases against that of a matched cohort of non-readmitted controls.

Methods

The study was a retrospective case-control study of patients 65 years or older admitted acutely for more than 24 h between 1 January 2005 and 31 December 2010 to the 75-bed general medicine service of a 640-bed tertiary hospital in Brisbane serving a population of 1 million in southeast Queensland.

Readmitted cases were patients discharged from and readmitted to the general medicine service under study within 30 days of discharge from index admission. They were selected on the basis of the most prevalent primary discharge diagnoses assigned to index admissions to the service during the study period. In descending order of frequency, these comprised heart failure, urinary tract infection, exacerbation of chronic obstructive pulmonary disease (COPD), cellulitis, chest pain, dementia or delirium, lower respiratory tract infection or pneumonia, sepsis, and syncope or collapse. Index admissions were randomly selected with a frequency distribution similar to that of primary discharge diagnoses, and all corresponding 30-day readmissions were identified.

Concurrent control patients who were not readmitted after index admission were selected if matched with readmitted patients on the basis of age, sex and principal discharge diagnosis of index admission. The aim was to have two control patients for every readmitted patient (2:1 ratio), but the number of available matches among all admissions during the study period restricted this ratio to 1.7:1.

As individual patients not admissions were the units of analysis, the index admission pertaining to an individual patient that was first selected during the study period resulted in censoring of any subsequent admissions that occurred after 30 days.

Hospital records of all selected patients were analysed independently by two reviewers – one for cases (HS), the other for controls (MA) – both reviewers being registrars who had completed 2 years of advanced training in general medicine within tertiary hospitals. Neither was involved in the care of study patients. Data were entered into a standardised database using explicit guidance from an abstraction manual, with pilot testing of the first 15 charts abstracted by each reviewer and cross-checked for accuracy by a senior consultant (IAS). Data were collected on patient clinical and demographic characteristics, discharge medications, length of hospital stays (LOS), discharge destination and 12 quality of care factors (Table 1) derived from previous studies.11,12,14 Given the multiplicity of different taxonomies of quality of care factors cited in the literature, we selected those factors that seemed to us to be the most clinically salient and which fitted into a framework that could guide targeted remedial strategies. Each patient could have one or more quality of care factors identified during index admission. The reviewers were instructed to use the ‘eyeball’ test in identifying quality of care factors, that is, those that were clearly evident from clinical information recorded in hospital charts, with no attempt made to second guess what had transpired. In the absence of validated algorithms, no attempt was made to gauge the propensity of identified factors to cause readmission or rate their level of preventability.

Variables were compared between readmissions and controls using chi-square tests, t-test and Mann–Whitney U-tests for proportions, normally and non-normally distributed data, respectively, with P-values <0.05 denoting statistical significance. Case and control patients who demonstrated one or more quality factors were compared with those for whom no quality of care factor was identified within their respective group. Reliability of detection of quality factors by the reviewers was assessed by level of agreement with a senior consultant (IAS) for

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factors identified among a random subset of 30 cases and 30 controls. This revealed moderate-to-good agreement: 89% for cases and 93% for controls; kappa = 0.47 (95% confidence interval (CI) 0.34–0.61) and 0.60 (95% CI 0.46–0.75) respectively.

As this study intended to assess quality of care using routinely collected data on completed episodes of care with reporting of anonymised data and no need for patient contact, ethical approval was not sought.

Table 1  Quality of care factors searched for during index admission

<table>
<thead>
<tr>
<th>Diagnostic error or failure to diagnose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic errors or avoidable failures to diagnose either primary presenting condition or associated abnormalities, for example evolutionary electrocardiogram changes with elevated troponin with no stated diagnosis of acute coronary syndrome; overlooked, new-onset, clearly abnormal biochemistry (e.g. serum sodium &lt;125 mmol/L) with no reference to cause.</td>
</tr>
<tr>
<td>Failure to assess or manage active comorbid disease</td>
</tr>
<tr>
<td>Failure to manage adequately active comorbidities that resulted in readmission, for example persistently elevated blood sugars (&gt;15 mmol/L) in a poorly controlled diabetic; significantly and persistently elevated blood pressure readings (systolic blood pressure &gt;180 mmHg).</td>
</tr>
<tr>
<td>Suboptimal management of primary clinical problem during admission</td>
</tr>
<tr>
<td>Failure to manage adequately the primary clinical problem, for example in a patient with heart failure no reference to salt and fluid restriction, commencement of angiotensin-converting enzyme inhibitor or β-blocker, investigation for precipitating causes for heart failure.</td>
</tr>
<tr>
<td>Potentially preventable complication of procedure or therapy undertaken/initiated during index admission</td>
</tr>
<tr>
<td>Newly administered therapy or a procedure undertaken during index admission inducing a new problem prompting readmission, for example hypoglycaemic episode following initiation of insulin therapy, sepsis resulting from an infected intravenous cannula site, symptomatic hypotension resulting from newly administered antihypertensives.</td>
</tr>
<tr>
<td>Inadequate assessment of needs and limitations</td>
</tr>
<tr>
<td>Failure to assess adequately needs and limitations, for example in a frail older patient, no assessment by allied health of physical and mental function and social support.</td>
</tr>
<tr>
<td>Inadequate patient/carer education about clinical management of disease</td>
</tr>
<tr>
<td>Failure to educate adequately patient and carers about the clinical management of disease, for example in a patient with poorly controlled diabetes no referral to a diabetic educator, in a patient with severe systolic heart failure no referral to a heart failure nurse.</td>
</tr>
<tr>
<td>Failure to communicate discharge information to post-hospital care providers</td>
</tr>
<tr>
<td>Failure to communicate adequately details of care to community-based or nursing home care providers, for example no discharge summary recorded, no entry under ‘referring doctor’, omission of important nursing or allied healthcare plans in discharge summary.</td>
</tr>
<tr>
<td>Failure to develop/activate advance care plan</td>
</tr>
<tr>
<td>Failure to formulate or activate advance care plan in eligible patients, for example in a patient with advanced multiorgan failure, or severe frailty or dementia, no mention of end of life care discussions or advance care plan in the event of future clinical deterioration.</td>
</tr>
<tr>
<td>Failure to develop/activate palliative care plan</td>
</tr>
<tr>
<td>Failure to formulate or activate palliative care plan for patients with clearly evident terminal illness, for example metastatic cancer with rapid downhill cause, bed-bound patient from high level nursing home with advanced dementia.</td>
</tr>
<tr>
<td>Failure to organise appropriate medical follow up</td>
</tr>
<tr>
<td>Failure to arrange follow up for patients who would reasonably require at least one review visit, for example to monitor effects of newly initiated or substantially altered therapy, follow up of key test results still pending at time of discharge.</td>
</tr>
<tr>
<td>Failure to refer to chronic disease management/outreach service where indicated</td>
</tr>
<tr>
<td>Failure to refer eligible patients to chronic disease management service (such as heart failure service, diabetes management programme), for example patients with severe systolic heart failure or poorly controlled diabetes with need for close surveillance, education and risk factor optimisation.</td>
</tr>
<tr>
<td>Failure to refer to rehabilitation programme (excluding geriatric rehabilitation) where indicated</td>
</tr>
<tr>
<td>Failure to refer eligible patients for rehabilitation, for example respiratory or cardiac rehabilitation for patients with chronic obstructive pulmonary disease or ischaemic heart disease respectively.</td>
</tr>
<tr>
<td>Failure to arrange required home assistance and community support</td>
</tr>
<tr>
<td>Failure to arrange support to patients requiring assistance or deemed eligible on assessment by allied health professionals.</td>
</tr>
</tbody>
</table>

Results

There were 113 readmitted cases and 198 controls whose characteristics are compared in Table 2. No significant differences were seen between groups in mean age, sex distribution, frequency of primary discharge diagnoses, LOS of index admission, number of discharge medications, discharge destination, marital status or baseline levels of functional impairment. Readmitted
cases demonstrated a significantly higher comorbidity burden than controls (mean ± standard deviation comorbidity score 6.6 (±2.2) vs 5.6 (±2.4, \(P = 0.003\)), more frequently had a non-English-speaking background (16.8% vs 9.1%, \(P = 0.046\)), and a greater proportion had one or more hospital admissions over the 6 months preceding index admission (55.7% vs 81.1%, \(P < 0.001\)). Half of the readmissions occurred within 11 days of discharge from index admission, three quarters within 18 days, and median readmission LOS was 6.0 days (interquartile range 3–13 days). Primary readmission diagnoses comprised exacerbation of chronic obstructive pulmonary disease (17, 15.0%), heart failure (12, 10.6%), chest pain/acute coronary syndrome (12, 10.6%), dementia/delirium (11, 9.7%), urinary tract infection (10, 8.8%), syncope/collapse/fall (7, 6.2%), cellulitis (5, 4.4%) and other (32, 28.3%).

Results of quality of care analyses during index admissions for both readmissions and controls are listed in Table 3, and illustrative cases are presented in Table 4. Among readmitted patients, 50 (44.3%) had one or more quality of care factors identified compared with 23 (11.6%) controls (\(P < 0.001\)). The most frequent quality factor among readmissions was failure to develop or activate an advance care plan (18, 15.9% vs 2, 1.0%; \(P < 0.001\)) in patients with end-stage disease for whom therapeutic options had been exhausted and who had often been admitted on multiple previous occasions for relapses of the same clinical condition (case 1, Table 4). Second in frequency was suboptimal management of the primary presenting clinical problem (13, 11.4% vs 0, 0%; \(P < 0.001\), manifesting predominantly as omission, underdosing or premature discontinuation of a treatment for which there was a strong indication (10, 8.8%, case 2). Third was inadequate assessment of patient care needs and functional limitations (11, 9.7% vs 0, 0%; \(P < 0.001\), case 3), spanning mobility and physical impairment (5, 4.4%), cognitive or psychological impairment (2, 1.8%), and limited home and community support (4, 3.5%). Fourth was a potentially preventable complication of a procedure or therapy undertaken or initiated during index admission that was either not indicated or not properly monitored (8, 7.1% vs 1, 0.5%, \(P = 0.002\), case 4). Fifth was failure to diagnose properly the presenting problem (8, 7.1% vs 0, 0%; \(P < 0.001\), case 5) mainly because of inadequate initial evaluation and problem synthesis related to faulty history taking or physical examination (7, 6.2%) rather than failure to order, interpret or follow up a diagnostic test result (1, 1.0%).

Less frequent quality factors were failure to recognise or fully assess active comorbid disease or condition (6, 5.3% vs 1, 0.5%; \(P = 0.010\), case 6), failure to develop or activate a palliative care plan in patients with imminent terminal illness (3, 2.6% vs 0.0%; \(P = 0.047\), case 7), and failure to refer to chronic disease management, outreach service or rehabilitation programme (3, 2.6% vs 4, 2.0%; \(P = 0.708\), case 8). In contrast with control patients, no instance was seen among readmitted patients of failure to communicate discharge summary or management plan to external care providers (0, 0% vs 11, 5.6%; \(P = 0.009\)) or failure to organise appropriate medical follow up (0, 0% vs 4, 2.2%; \(P = 0.301\)).

Among readmitted patients, there were no significant differences between those demonstrating quality factors (\(n = 50\)) and those that did not (\(n = 63\)) in terms of age, sex, index admission or readmission LOS, time to readmission, ethnicity, site of residence, number of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 113)</th>
<th>Controls (n = 198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>80.0 ± 7.8</td>
<td>79.3 ± 8.0</td>
</tr>
<tr>
<td>Male/female</td>
<td>56/57</td>
<td>92/106</td>
</tr>
<tr>
<td>LOS index admission (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>5.7 ± 4.5</td>
<td>6.3 ± 5.6</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5.0 (3–7)</td>
<td>4.0 (2–7)</td>
</tr>
<tr>
<td>Marital status (M/S)</td>
<td>41/72</td>
<td>53/145</td>
</tr>
<tr>
<td>Discharge diagnosis index admission (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>21 (18.6)</td>
<td>40 (20.2)</td>
</tr>
<tr>
<td>UTI</td>
<td>20 (17.7)</td>
<td>30 (15.1)</td>
</tr>
<tr>
<td>COPD</td>
<td>17 (15.0)</td>
<td>34 (17.1)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>14 (12.4)</td>
<td>26 (13.1)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>12 (10.6)</td>
<td>14 (7.1)</td>
</tr>
<tr>
<td>Dementia/delirium</td>
<td>12 (10.6)</td>
<td>21 (10.6)</td>
</tr>
<tr>
<td>LRTI/pneumonia</td>
<td>11 (9.7)</td>
<td>26 (13.1)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3 (2.6)</td>
<td>5 (2.5)</td>
</tr>
<tr>
<td>Syncope/collapse</td>
<td>3 (2.6)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Residing in nursing home (%)</td>
<td>30 (26.5)</td>
<td>51 (25.8)</td>
</tr>
<tr>
<td>Comorbidity score</td>
<td>Mean ± SD</td>
<td>6.6 ± 2.0</td>
</tr>
<tr>
<td>Medications at index discharge</td>
<td>Mean (±SD)</td>
<td>8.7 ± 4.6</td>
</tr>
<tr>
<td>Non-English-speaking background (%)</td>
<td>19 (16.8)</td>
<td>18 (9.1)**</td>
</tr>
<tr>
<td>Admission within 6 months prior to index admission (%)</td>
<td>63 (55.7)</td>
<td>16 (8.1)*</td>
</tr>
<tr>
<td>Level of functional impairment on presentation index admission (%)†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
comorbidities, or discharge medications (data not shown). Similar null findings were seen when comparing control patients with \((n = 23)\) and without \((n = 175)\) quality factors (data not shown). Primary readmission diagnoses related to the index admission diagnosis were seen more often in the 50 patients demonstrating quality factors \((33/50 (66\%) \text{ vs } 26/63 (41\%); \text{ } P = 0.002)\).

**Discussion**

Our study reveals potentially preventable quality of care factors involving 44% of readmitted patients compared with 12% of matched controls who were not readmitted. Deficiencies in advance care planning, management of presenting clinical condition, assessment of functional limitations and initial diagnostic evaluation were the most commonly identified problems among readmitted patients.

Among controls, the most frequent quality factor was lack of discharge communication that we surmise may relate to medical staff perceiving these patients as having less need for early postdischarge care from community providers on the basis of fewer comorbidities and past hospitalisations, and hence less requirement for discharge documentation.

**Study limitations**

While our study identified quality of care factors associated with readmissions, we cannot infer a causal relationship that implies that all or any of these readmissions were definitely or probably avoidable. The retrospective review of hospital charts and identification of quality factors depended on what was recorded in charts and how it was subjectively interpreted by the reviewers who were not blind to readmission status or primary readmission diagnoses, and to whom, for logistical reasons, charts of cases and controls were not randomly assigned. Consequently, cuing or hindsight bias cannot be excluded, although a structured abstraction method was used. Having only one reviewer for each chart may also bias towards underdetection of preventable readmissions, and the level of agreement between reviewers and a senior consultant was only moderate. Only same-hospital, same-service readmissions were considered due to the absence of unique personal identifiers that track individual patients across all Queensland hospitals, and the need to match optimally cases with controls. Both limitations potentiate detection bias compared with assessing all-hospital, all-service readmissions.23

Study strengths are the representative sampling of readmissions and controls according to prevalence of discharge diagnoses and close matching of both groups that minimised potential bias towards overestimating quality factors in readmitted cases simply by virtue of older age, greater comorbidity or disease severity. A case–control design also allowed differentiation between readmitted and non-readmitted patients in the types and frequency of quality factors.

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**Table 3** Frequency of quality of care factors

<table>
<thead>
<tr>
<th>Quality of care factor</th>
<th>Cases (n = 113)</th>
<th>Controls (n = 198)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more quality of care factors identified</td>
<td>50 (44.3)</td>
<td>23 (11.6)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Complication of procedure or therapy undertaken/initiated during index admission</td>
<td>8 (7.1)</td>
<td>1 (0.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diagnostic error or failure to diagnose</td>
<td>8 (7.1)</td>
<td>0 (0)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Inadequate initial evaluation</td>
<td>7 (6.2)</td>
<td>0 (0)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Failure to request/interpret/follow-up diagnostic test result</td>
<td>1 (0.9)</td>
<td>0 (0)</td>
<td>0.343</td>
</tr>
<tr>
<td>Failure to recognise or fully assess active comorbid disease</td>
<td>6 (5.3)</td>
<td>1 (0.5)</td>
<td>0.010</td>
</tr>
<tr>
<td>Suboptimal management of primary clinical problem during index admission</td>
<td>13 (11.4)</td>
<td>0 (0)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Inappropriate drug use or monitoring</td>
<td>3 (2.6)</td>
<td>0 (0)</td>
<td>0.047</td>
</tr>
<tr>
<td>Indicated drug omitted or stopped prematurely</td>
<td>10 (8.9)</td>
<td>0 (0)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Inadequate assessment of needs and limitations</td>
<td>11 (9.7)</td>
<td>0 (0)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Failure to assess mobility/physical disability</td>
<td>5 (4.4)</td>
<td>0 (0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Failure to assess cognitive/psychological impairment</td>
<td>2 (1.8)</td>
<td>0 (0)</td>
<td>0.131</td>
</tr>
<tr>
<td>Failure to assess need for home/community support</td>
<td>4 (3.5)</td>
<td>0 (0)</td>
<td>0.017</td>
</tr>
<tr>
<td>Inadequate patient/carer education about clinical management of disease</td>
<td>2 (1.8)</td>
<td>1 (0.5)</td>
<td>0.299</td>
</tr>
<tr>
<td>Failure to communicate discharge summary/management plan to post-hospital care providers</td>
<td>0 (0)</td>
<td>11 (5.6)</td>
<td>0.009</td>
</tr>
<tr>
<td>Failure to develop/activate advance care plan</td>
<td>18 (15.9)</td>
<td>2 (1.0)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Failure to develop/activate palliative care plan</td>
<td>3 (2.6)</td>
<td>0 (0)</td>
<td>0.047</td>
</tr>
<tr>
<td>Failure to organise appropriate medical follow up</td>
<td>0 (0)</td>
<td>4 (2.2)</td>
<td>0.301</td>
</tr>
<tr>
<td>Failure to refer to chronic disease management/outreach service/rehabilitation programme where indicated</td>
<td>3 (2.6)</td>
<td>4 (2.2)</td>
<td>0.708</td>
</tr>
<tr>
<td>Failure to arrange required home assistance and community support</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

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As noted by other investigators, the numbers of comorbidities and previous acute hospitalisations were predictors of readmission risk. While the proportion of readmissions in our cohort associated with quality of care factors may seem unduly high, other studies of unplanned readmissions involving older medical patients have reported comparable figures, albeit with considerable between-study variation in both the

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### Table 4 Illustrative case studies of quality of care factors

**Failure to develop or activate advance care plan**

Case study 1: 73-year-old woman presents with acute cardiac failure secondary to ischaemic cardiomyopathy (LV ejection fraction 30%), severe COPD requiring home oxygen and steroid dependent myasthenia gravis. This is her fifth admission in the past 12 months. She responds to diuretic therapy but represents 4 days later with another episode of cardiac decompensation despite maximal medical therapy, precipitated by *Escherichia coli* urosepsis and deceases in hospital on day 2.

**Failure to manage optimally primary presenting complaint**

Case study 2: 82-year-old woman presents with acute cellulitis of the left lower limb and is treated with intravenous flucloxacillin followed by oral equivalent for 10 days after discharge. Her fever on admission quickly subsides although leg erythema and tenderness persists. She represents 6 days later with recurrent leg swelling, redness and fever, and is treated with intravenous lincomycin. Despite negative blood cultures on index admission, her CRP level had increased from 77 to 217 at time of discharge suggesting ongoing infection.

**Failure to assess fully functional needs and limitations**

Case study 3: 79-year-old woman presents with acute non-cardiac chest pain and delirium and is noted to be hyponatraemic (Na 117), presumed secondary to either or both lithium therapy for bipolar affective disorder and SIADH secondary to severe emphysema. Her delirium resolves with normalisation of her sodium level, and she is discharged after 48 h but represents 3 weeks later with erratic behaviour and ongoing confusion. CT head scan reveals marked cerebral atrophy and small vessel white matter ischaemia. Family members indicate deteriorating function in activities of daily living over several months and ‘underlying dementia’ had been flagged as a possible diagnosis during previous admission, associated with normal dementia screen. Her carer husband had been hospitalised a few days prior to readmission, possibly precipitating her confusional state. Formal testing of cognitive function and occupational therapist assessment were omitted during index admission.

**Complication of therapies initiated during index admission**

Case study 4: 87-year-old man with past right brachial artery embolus requiring embolectomy and chronic warfarin therapy presents with Klebsiella UTI. He receives intravenous gentamicin and is discharged 3 days later on oral augmentin with INR at discharge of 3.2 compared with 2.4 on admission. He is referred back 9 days later following a second course of antibiotic with INR of 5.6 but no overt bleeding. Closer monitoring of INR and reduction of warfarin dose may have prevented this readmission.

**Diagnostic error involving index admission**

Case study 5: 93-year-old nursing home resident with past depression presents with agitated behaviour diagnosed as hyperactive delirium because of mild hyponatraemia (Na 117), UTI and recently commenced psychotropic medication for depression. She responds to fluid restriction and antibiotics, and is discharged. Psychogeriatric assessment is of mixed delirium and depression, and follow up is arranged. She represents 3 weeks later with panic attacks, obsessive compulsive behaviour and worsening depression. Undue emphasis may have been given to delirium rather than underlying mental illness in her initial presentation.

**Failure to identify and manage active comorbid problem**

Case study 6: 73-year-old woman is discharged on antibiotics following a syncopal episode induced by hypovolaemia secondary to gastroenteritis complicated by UTI. New onset hyponatraemia (Na 125), UTI and recently commenced psychotropic medication for depression. She responds to fluid restriction and antibiotics, and is discharged. Psychogeriatric assessment is of mixed delirium and depression, and follow up is arranged. She represents 3 weeks later with recurrent decompensated heart failure secondary to chronic obstructive sleep apnoea and LV dysfunction (ejection fraction 35%). His history, combined with ward observations, suggest non-compliance with fluid restriction and diuretic therapy, compounded by social isolation and limited ability to speak English. At discharge, no referral is made to the heart failure outreach service, and he represents with recurrent decompensated heart failure and acute cardiorenal syndrome secondary to continuing non-compliance.

**Failure to develop or activate palliative care plan**

Case study 7: 88-year-old fully dependent nursing home resident with severe advanced dementia and stage 4 chronic kidney disease is transferred to hospital with E. coli urosepsis. In the absence of both an advance health directive and an enduring power of attorney, intravenous fluids and antibiotics are administered with transfer back to the nursing home 3 days later, but with no palliative care plan, should she develop further acute illness. Six days later, she is re-referred with recurrent urosepsis and is again resuscitated, but she refuses all food and medications. After her family agrees to conservative measures, she is transferred back to the nursing home and dies 1 week later.

**Failure to refer to chronic disease management, outreach service or rehabilitation programme**

Case study 8: 84-year-old man presents with decompensated biventricular heart failure secondary to recurrent pulmonary thromboembolism, obstructive sleep apnoea and LV dysfunction (ejection fraction 35%). His history, combined with ward observations, suggest non-compliance with fluid restriction and diuretic therapy, compounded by social isolation and limited ability to speak English. At discharge, no referral is made to the heart failure outreach service, and he represents with recurrent decompensated heart failure and acute cardiorenal syndrome secondary to continuing non-compliance.

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COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; GP, general practitioner; INR, international normalised ratio; LV, left ventricular; SIADH, syndrome of inappropriate antidiuretic hormone; UTI, urinary tract infection.

**Comparison with similar studies**

As noted by other investigators, the numbers of comorbidities and previous acute hospitalisations were predictors of readmission risk. While the proportion of readmissions in our cohort associated with quality of care factors may seem unduly high, other studies of unplanned readmissions involving older medical patients have reported comparable figures, albeit with considerable between-study variation in both the
estimates of the preventable fraction and the type and frequency of putative quality of care factors.

In one study of 811 readmissions to Veterans Affairs hospitals, 34% were deemed potentially preventable, of which one-third was attributed to inadequate assessment or treatment.\(^{25}\) In a case–control study of 271 readmissions to a tertiary hospital that involved patient interviews, 33% were deemed preventable compared with 6% of controls, with incomplete initial work-up, inappropriate medication, diagnostic error and premature discharge being proposed as causative factors.\(^{26}\) In a prospective study of 133 readmissions to a geriatric unit that involved interviews of clinician and patients, 59% were deemed potentially preventable by way of better preparation for discharge, greater attention to carer needs, more timely and adequate information to general practitioners, and better medication management.\(^{27}\) In another prospective study of 537 readmissions using chart reviews, patient and clinician interviews and overall case assessment by a nurse-physician team, 47% were deemed potentially preventable, with lack of advance care planning and end-of-life care noted in nearly half the cases, while suboptimal management of presenting complaint or active comorbidity, inadequate discharge planning, and inappropriate drug prescribing comprised other contributory factors.\(^{28}\) In another study, 50% of 154 readmissions in older patients were judged potentially preventable mainly through improved patient education and discharge planning.\(^{29}\)

While studies are few, readmissions to subspecialty units also demonstrate similar problems. A retrospective chart review of 39 readmitted patients discharged from a heart failure unit revealed 39% were potentially preventable as a result of suboptimal participation in chronic disease management.\(^{30}\) Patients discharged from cardiology units following acute myocardial infarction show deficiencies pertaining to multidisciplinary team care, medication reconciliation and discharge communications.\(^{31}\) In a retrospective study of 165 patients with cirrhosis readmitted to hepatology units, 22% were deemed preventable because of failures in therapeutic titration and monitoring, and failure to plan for future contingencies.\(^{32}\)

The low prevalence in our study of quality factors (other than discharge communication) among controls, compared with readmitted cases, deserves further comment. While such a disparity has been noted in another case–control study of similar patients,\(^{26}\) it may reflect the previously mentioned biases peculiar to the assessment of readmitted cases. Our use of an unambiguous ‘eyeball’ test of quality may also have led to undercalling of more subtle quality factors among controls, although regularly monitored quality indicators relating to the study service\(^{13}\) suggest a high level of performance.

**Implications for clinical practice**

Throughout 2011/12, 30-day readmission rate of 12% for acute discharges from the study service approximated those reported from similar general medicine services in 10 other Australian tertiary hospitals that ranged from 9% to 14%.\(^{34}\) At a state level, 2012/13 data from the Queensland Health Statewide General Medicine Clinical Services Network reported 28-day readmission rates for acute discharges from general medicine units of all five tertiary hospitals in that state (including study hospital) ranging from 10% to 15% on a monthly basis.\(^{35}\) These observations confirm the service under study is not an outlier in terms of unplanned readmissions.

Correcting quality of care factors involving readmitted cases problems may reduce the risk of readmission, although to what extent remains unclear. Older, frail patients with complex needs and underlying advanced chronic disease will inevitably have a high propensity for repeated hospitalisations despite optimal care\(^{40}\) and overzealous, penalty-driven efforts to reduce readmissions in this highly vulnerable group may result in unintended adverse outcomes.\(^{36}\) However, discharges occurring within a week after discharge, which comprised one-third of readmissions in our cohort, are more likely to reflect deficiencies in peridischARGE care, whereas those more distant are more likely to reflect underlying disease severity. If at least one-third of these potentially avoidable admissions could be prevented, this would reduce the overall readmission rate by 15%.\(^{37}\) Such a saving provides sufficient impetus to consider strategies for improving quality of peridischARGE care.

Our findings are notable in several respects. The most prevalent quality of care factor was the absence of advanced care plans (ACP) in 16% of readmitted cases, a finding reported in few other studies.\(^{28}\) While our results may reflect an older, multimorbid population, we suspect prior studies failed to regard ACP as an important part of transition care – an omission now attracting attention\(^{44}\) given the potential of ACP to promote earlier initiation of more appropriate palliative care and reduce the total time spent in hospital.\(^{39-41}\) In particular, studies involving nursing home residents, who comprised a quarter of our cohort, show 40–80% reductions in rates of hospitalisation and up to threefold increase in palliative care referrals resulting from advance care plans or directives.\(^{42,45}\)

Suboptimal management of presenting complaints (11%), diagnostic errors (7%) and failure to treat appropriately active comorbidities (5%) comprised problems relating to acute care that have been reported in other studies.\(^{25,26,28}\) These may reflect the fact that acute illness in older patients often presents atypically and on a background of multiple, active comorbidities.\(^{46}\) Synthesising
accurate diagnostic formulations and management plans amid such uncertainty and complexity is challenging. Checklists, algorithms, mnemonics and care pathways that are specific to the evaluation and treatment of older patients may reduce the incidence of such failures.

Inadequate assessment of functional needs and limitations seen in 10% of readmissions has been observed in other studies, despite the general medicine service under study being cognisant of all key principles of gerontological care and liaising closely with geriatricians. Formal geriatric evaluation and management (GEM), either as consultative GEM teams or admission to dedicated GEM units, has not been shown in systematic reviews to decrease readmission rates compared with usual care. Similarly, postdischarge specialist geriatric medical assessment or intensive, community-based case management has no impact.

Evidence suggests readmission rates may reduce with transitional care strategies that integrate predischarge needs assessment and patient/carer education in self-management with postdischarge home visits, telephone support and service coordination, supervised by a dedicated discharge coordinator or transitional ‘coach’ or ‘navigator’. Such ‘bridging’ programmes include the Transitional Care Model, the Care Transitions Intervention, and Project Better Outcomes for Older adults through Safe Transitions. These comprehensive patient-centred approaches surpass standard and fragmented disease-focused interventions and can decrease readmissions by between 10% and 25%. However, such programmes are resource-intensive, are subject to inconsistent implementation and may not reduce readmissions associated with acute care deficiencies in the initial days of hospitalisation. Nevertheless, a recent study stressed the need to focus on co-morbidities as readmissions often relate to complications of co-morbidities. Moreover, high performing hospitals with lower than average readmission rates exhibit rates that are independent of index or readmission diagnoses as a result of global rather than diagnosis-specific strategies for reducing readmissions.

Conclusion

Unplanned readmissions involving older medical patients appear to be associated with more quality of care problems during index admission than a similar cohort of non-readmitted patients, with omission of advance care planning being the predominant failing. Correcting these problems may reduce the risk of readmission, although the propensity for readmission of older, frail patients with advanced diseases and multimorbidity will inevitably remain high despite optimal care.

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Quality of care and readmissions


Utilisation of beds on the general medical unit by ‘non-acute medical’ patients: a retrospective study of incidence and cost in two Tasmanian regional medical hospital units

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Key words
inappropriate admission, medical unit, regional Australia, cost analysis.

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Abstract
Background: Demand for healthcare services threatens to overwhelm the Australian healthcare system. Public hospitals have the largest component of expenditure growth and as such represent the largest opportunity for efficiency gains. Utilisation of inpatient hospital beds and in particular those on general medical units has not been studied in Australia.

Aim: To undertake a retrospective patient medical record review of 200 sequential admissions to the medical wards in two regional Tasmanian hospitals to determine the incidence of non-acute medical patient admission to the medical unit, and the subsequent days in hospital that were not required for medical reasons. The cost of these days was estimated.

Results: Sixteen patient admissions (8%) could not be justified on medical grounds. Forty-eight (24%) patient admissions had at least one day hospital day that could not be justified on medical grounds. Of the 1438 total bed days, 475 (33%) were for non-medical reasons. The estimated cost of those non-medical bed days for this cohort was $764 800.

Conclusions: The incidence of non-acute medical admissions and non-acute medical bed days to the medical unit and associated cost was significant. Further research is needed to design alternative care provision for such patients particularly in regional Australia. The potential savings to the Australian healthcare system could be significant.

Introduction
Expenditure on health in Australia has increased from $72.2 billion in 1999–2000 to $121.4 billion in 2009–2010 and as a proportion of gross domestic product has gone from 7.9% to 9.4% in this period.1 Spending on public hospital services in 2009–2010 was estimated at $36.2 billion or 31.2% of total recurrent health expenditure.1 As population growth persists and the rate of ageing accelerates, demand for healthcare will increasingly burden the capacity of the current Australian healthcare system.1,2 By 2050 also, if existing hospital bed use trends continue in a context of exponential rises in frail older patients, a 62% increase in hospital beds will be needed to meet the projected demand – costing almost as much as the current budget for the entire system of healthcare in Australia.3 At the same time, over the last quarter of a century in Australia, the total number of acute public hospital beds has decreased by a third, from 74 000 beds (1983) to 56 900 beds in 2009–2010.4 This translates into a 60% fall, adjusted for population growth, from 4.8 public acute beds per 1000 population in 1983 to 2.5 per 1000 population (2.6 per 1000, including psychiatric beds).4 Yet it is also known that public hospital bed availability varies throughout Australia: regional, rural and remote areas have more public hospital beds available per 1000 population than urban areas.4 However, these tend to be of lower acuity, having limitations in resources and clinical skills sets compared with metropolitan tertiary hospitals.
Public hospitals consume the highest percentage of health-dollars and were the largest component of the increase in healthcare expenditure in 2009–2010. As such, they possibly represent the largest opportunity for efficiency gains. Strategies to enhance the cost-efficiency of hospitals have largely focused on activity based funding arrangements and incentivised funding schemes for politically sensitive clinical areas, notably emergency department waiting times and elective surgical waiting lists. Minimal attention has been drawn to the efficiency of medical inpatient units. These units account for greater than one half of hospitals’ clinical and fiscal activity, and are disproportionately occupied by elderly patients with a high incidence of age-related complex, chronic disease processes.

International studies have found a significant incidence of both inappropriate admission to an acute hospital bed and subsequent rate of inappropriate hospital bed day utilisation postadmission. None of these studies have been performed in Australia, and most were done in metropolitan teaching hospitals. Only one study included a financial analysis of the inappropriate bed days.

Thus, we undertook a study that had two aims: first, to measure retrospectively the incidence of non-acute medical admissions, and bed days, at two regional Tasmanian hospitals and, second, to do an economic evaluation of these admissions and bed days.

**Methods**

**Study setting**

The North West Area Health Service (NWAHS) services a population of 113,000 in a geographic area that encompasses the North and remote West Coasts of Tasmania and King Island. There are two acute hospitals: the North West Regional Hospital (NWRH) at Burnie and the Mersey Community Hospital (MCH) at Latrobe but with service to the greater Devonport area. Excluding mental health and obstetric beds NWRH had 130 beds and MCH 70 beds at the time of the study.

**Study design**

We conducted a retrospective cohort study of 100 sequential patients that were admitted each to the acute general medical unit from the hospital emergency departments from 1 July 2010. Each hospital admission was classified as being either medically required, not medically required or a result of a combination of medical and social factors. Medical factors were determined by documentation of an actual medical condition or diagnosis as the reason for admission to hospital. This was confirmed by a treatment plan that included medical therapies such as antibiotics or intravenous fluid to treat conditions, such as pneumonia or pyelonephritis. Likewise, social factors that determined admission were again determined by documentation in the medical record of situations where most commonly the patient could not manage at home by themselves or with whatever supports and care packages were in place. Similarly, each hospital bed day was classified as being medically required or not medically required based on retrospective review of the assessment made of the patient’s condition by the treating medical team, as documented in the medical record. Bed days deemed not required were those when no further active medical treatment or investigation was required, or that the patient was ready for discharge. Bed days that were assessed as having both medical and social contributions were classified as medically required.

The retrospective review of the patient medical records was undertaken as a two-stage procedure. The trained research assistant screened all the medical record documentation for each case. All hospital admissions and bed days that from the nursing and medical entries were clearly medically required were counted as such. All medical records where this distinction was not clear or from the documentation it appeared that a bed day was not medically required were reviewed by a specialist physician (M. B.). The classification by this physician was made only on the documentation of requirement for hospital admission or bed day and not on the opinion of appropriateness of that decision. The medical bed-day cost used was $1600 per day. This was based on the National Hospital Cost Data Collection results from Round 14 (2009–10) for NWAHS Hospitals (Burnie and MCHs). Expenditure (cost) is allocated to the patient from the actual pathology and radiology costs are allocated to the patient from the actual pathology and radiology costs are allocated to the patient from the actual costs from the private provider.

Approval for this study to be undertaken was granted by the Tasmanian Health and Research Ethics Committee.

**Data collection and statistical analysis**

Data were collected by review of the medical record and by accessing routinely available NWAHS data and then...
entered into an excel spreadsheet. All data were imported into IBM SPSS version 19 (IBM, Armonk, NY, USA) for analysis and examined with descriptive and frequency analyses. Pearson’s chi-square test was used to investigate associations between categorical variables, except for tests with cell frequencies less than 5, in which case the Fischer’s exact test was used. Non-parametric continuous data were transformed to approximate a normal distribution, and t-tests were used to detect differences in means. All tests were two sided, and differences were accepted as significant at $P < 0.05$ level.

**Results**

Of the 200 patient admissions in this study, 174 (87%) were deemed to have an acute medical illness that required admission to hospital under the treating medical unit (Fig. 1). Twenty-two (11%) of these patients subsequently had hospital admission days that were deemed not to be medically required by their treating medical team. Sixteen (8%) patients were admitted to hospital with no justification for a medical admission, and a further 10 (5%) patients were admitted with a medical diagnosis, but also with considerable situational issues that mandated admission. Overall, 48 patients (24%) were either admitted with no acute medical condition or at some point in their hospital stay accumulated bed days that the treating medical team could not justify. Of the total number of bed days (1438) accrued by the 200 patients in this study, 33% were deemed to be unnecessary on medical grounds as stated in the patient medical record. Taking the medical bed day cost of $1600, the total cost of these unnecessary bed days for the cohort of 200 patients was $764 800.

Table 1 lists the patient demographics, status at hospital admission, most common admission diagnosis, length of hospital stay, discharge diagnostic related group and discharge destination for the different patient groups in the study. Table 2 is a comparison of the patients without sufficient clinical grounds for admission with patients admitted on the basis of an acute medical condition. There were no statistically significant differences against the criteria listed in Table 1. However, there were some important differences that did not reach significance. These patients showed a trend to be less likely to be discharged home (56.3% vs 75.5%, $P = 0.13$) and more likely to die (12.5% vs 3.8%, $P = 0.16$) in the hospital or be discharged to a residential care facility for permanent placement (18.8% vs 4.3%, $P = 0.05$).

---

**Medical Requirement for Admission**

<table>
<thead>
<tr>
<th>Patients who had medically inappropriate hospital days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$n = 200$</strong></td>
</tr>
<tr>
<td>174 (87%) Appropriate</td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td>10 (5%) Medical and other reason</td>
</tr>
<tr>
<td>16 (8%) Inappropriate</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>16</td>
</tr>
</tbody>
</table>

**Figure 1** Classification of patients at admission and subsequent bed days.

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Discussion

Main findings

The main findings of the study are that one third of the total medical bed days were assessed as not being required. While not statistically significant, we argue that when taken together, the three differences observed suggest that these patients were more likely to be transitioning to long-term care, or at least a proportion of them were. Their level of frailty may have precipitated admission in the absence of available alternative and more appropriate facility.

The hospital costs for the 200 patients in this cohort was $764 800. Extrapolating this using 2011 medical unit admission data at both hospitals would give an estimated annual cost for inappropriate bed days of $8.4 million or approximately 5% of total budget for the area Health Service. Savings would still be made if these admissions were to care facilities with lower costs per patient, per day. These results were obtained by a detailed case note review and correlation of these data with the NWAHS business intelligence unit.

Study limitations

First, the main limitation of this study was that the determination of ‘acute medical condition’ was dependent on the accuracy of medical notes and of the judgements made by both the attending clinicians and of the physician reviewer. In particular, the physician review was conducted retrospectively with the benefit of hindsight and, in the absence of prospective validation of the means used by the expert reviewer in judging ‘acute medical condition’, may have biased towards overestimates in categorisation of non-acute medical admissions or bed days or both. Two explicit instruments used most commonly to assess appropriateness of hospital stays are

Table 1 Patient characteristics by admission classification

<table>
<thead>
<tr>
<th></th>
<th>Medically acute admission (n = 150)</th>
<th>Non-medical admission (n = 16)</th>
<th>Both (n = 10)</th>
<th>Medically acute admission and non-medical days (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) or mean ± SD</td>
<td>n (%) or mean ± SD</td>
<td>n (%) or mean ± SD</td>
<td>n (%) or mean ± SD</td>
</tr>
<tr>
<td>Age</td>
<td>66.8 ± 17.4</td>
<td>74.0 ± 16.9</td>
<td>81.6 ± 5.9</td>
<td>78.5 ± 15.7</td>
</tr>
<tr>
<td>Women</td>
<td>69 (45.0)</td>
<td>10 (62.5)</td>
<td>4 (40.0)</td>
<td>10 (45.5)</td>
</tr>
<tr>
<td>Living situation prior to admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residential aged care facility</td>
<td>6 (3.9)</td>
<td>2 (12.5)</td>
<td>0</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Living at home alone</td>
<td>41 (27.0)</td>
<td>4 (25.0)</td>
<td>7 (70.0)</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>Living at home with others</td>
<td>105 (69.1)</td>
<td>10 (62.5)</td>
<td>3 (30.0)</td>
<td>12 (54.5)</td>
</tr>
<tr>
<td>Admission diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16 (10.5)</td>
<td>0</td>
<td>0</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>COPD with acute exacerbation or infection</td>
<td>11 (7.2)</td>
<td>1 (6.3)</td>
<td>1 (10.0)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>UTI</td>
<td>7 (4.6)</td>
<td>1 (6.3)</td>
<td>0</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8 (5.3)</td>
<td>0</td>
<td>0</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6 (3.9)</td>
<td>0</td>
<td>1 (10.0)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Angina</td>
<td>9 (5.9)</td>
<td>0</td>
<td>1 (10.0)</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2 (1.3)</td>
<td>2 (12.5)</td>
<td>0</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Syncope and collapse</td>
<td>5 (3.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cellulitis of lower limb or trunk</td>
<td>3 (2.0)</td>
<td>0</td>
<td>1 (10.0)</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral infarction, unspecified</td>
<td>2 (1.3)</td>
<td>0</td>
<td>0</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Hypo-osmolality and hyponatraemia</td>
<td>4 (2.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4 (2.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Viral meningitis</td>
<td>4 (2.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total days in hospital</td>
<td>4.9 ± 5.8</td>
<td>8.2 ± 9.7</td>
<td>16.0 ± 9.0</td>
<td>18.6 ± 18.9</td>
</tr>
<tr>
<td>Discharge destination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>4 (2.6)</td>
<td>2 (12.5)</td>
<td>0</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Home</td>
<td>120 (78.9)</td>
<td>9 (56.3)</td>
<td>6 (60.0)</td>
<td>13 (59.1)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.3)</td>
<td>0</td>
<td>0</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Permanent placement aged care</td>
<td>0</td>
<td>3 (18.8)</td>
<td>4 (40.0)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Respite</td>
<td>1 (0.7)</td>
<td>1 (6.3)</td>
<td>0</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Transferred to another hospital</td>
<td>22 (14.5)</td>
<td>1 (6.3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; SD, standard deviation; UTI, urinary tract infection.
the appropriateness evaluation protocol\textsuperscript{29} and the Intensity of Service, Severity of Illness, Discharge Screens, a commercial product from the InterQual products Group.\textsuperscript{30} However, the validity of such instruments when compared with expert panel review has been found to be poor.\textsuperscript{31} Second, this is an isolated retrospective study in two Tasmanian regional hospitals. Among Australian states and territories, Tasmania has the oldest median age of 39.9 years and the equal (with South Australia) highest proportion (15.6\%) of people aged 65 years and over. Tasmania also has had the biggest increase in this aged population demographic between 2005 and 2010.\textsuperscript{32} As such, the incidence of patients with chronic- and complex age-associated conditions may be more common in these two hospitals, possibly giving rise to an increased incidence of inappropriate bed days. Lastly, there has been no internal or external validation of the bed day cost of $1600.\textsuperscript{28} This may reflect inefficiency in the service delivery rather than optimal price for the service.\textsuperscript{6}

**Implications for clinical practice and healthcare policy**

The significance of this study is that while the importance of inappropriate bed use as a policy issue is well known,\textsuperscript{6} little is known about the extent of the problem in rural and regional hospital settings. Importantly, the relationship between inappropriate bed utilisation and patient bed days that are not medically required is complex and may relate more to factors beyond the control of the treating medical teams. In particular in rural and regional settings, discharge planning can be hampered by the distance between the patients’ home and hospital and community services. This study suggests that inappropriate bed use may be at least as high in regional hospitals as other settings and raises the question of whether regional hospitals serving rural communities may have even higher inappropriate bed use than urban hospitals. Effective use of those limited resources is critical in order to maximise appropriate health service delivery and optimise health outcomes.

Clinical process redesign in hospitals and capacity building of non-hospital care services such as residential aged care services are known to be effective strategies to improve hospital bed utilisation.\textsuperscript{3} However, rural and regional communities may have compromised capacities in the latter especially. Notwithstanding, relatively simple measures, such as physician direct accountability tools supporting physician audits of patient hospital stays, have been shown to be effective in reducing excessive hospital bed use\textsuperscript{33} and have fairly direct applicability to rural and regional settings. While the literature suggests that there are savings to be made by developing different models of care delivery,\textsuperscript{11,34} more work needs to be done to explore whether and how specific service strategies would work in the distinctive settings of rural and regional hospitals.

Investing in chronic disease management programmes is also known to be an effective strategy in reducing inappropriate use of hospital beds.\textsuperscript{3} However, rural and regional communities lack the critical mass of allied healthcare practitioners and community services that can help make self-management programmes effective. There are strong arguments that policy makers’ preferences for

---

**Table 2** Comparison of non-medical admissions versus other patient admission categories

<table>
<thead>
<tr>
<th></th>
<th>Non-medically acute admission (n = 16)</th>
<th>Other admission categories (n = 184)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>81 (64.0–86.8)</td>
<td>74 (59.0–82.0)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>6 (37.5)</td>
<td>87 (47.3)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Living situation prior to admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residential aged care facility</td>
<td>2 (12.5)</td>
<td>7 (3.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Living at home alone</td>
<td>4 (25.0)</td>
<td>57 (31.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>Living at home with others</td>
<td>10 (62.5)</td>
<td>120 (65.2)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Total days in hospital</strong></td>
<td>6.0 (3.3–8.8)</td>
<td>4.0 (3.0–7.0)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Discharge destination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>2 (12.5)</td>
<td>7 (3.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>Home</td>
<td>9 (56.3)</td>
<td>139 (75.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>6 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Permanent placement aged care</td>
<td>3 (18.8)</td>
<td>8 (4.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Respite</td>
<td>1 (6.3)</td>
<td>2 (1.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>Transferred to another hospital</td>
<td>1 (4.3)</td>
<td>22 (12.0)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

---, Insufficient numbers for statistical analysis; IQR, interquartile range.
non-hospital-based solutions to managing acute hospital bed shortages are not evidence based and inadequately account for the limits of prevention and primary healthcare.4

Conclusion
Our results suggest that the rural and regional hospital system is not effectively answering the question ‘Does this person need to be in hospital?’ Inappropriate bed use should be a policy priority for rural and regional healthcare in particular and be addressed at the whole-of-system level.

Acknowledgements
The Business Intelligence Unit of the NWAHS and in particular their Director Simon Foster provided the costing data and assistance with the data collection. Penny Allen from the University of Tasmania Rural Clinical School provided statistical support to analyse the data.

References
Prescribing for comorbid disease in a palliative population: focus on the use of lipid-lowering medications

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Key words
palliative care, physician prescribing pattern, comorbidity, polypharmacy, lipid-regulating agent, prevention.

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Abstract

Background: The balance of benefit versus burden of ongoing treatments for comorbid disease in palliative populations as death approaches needs careful consideration given their particular susceptibility to adverse drug effects.

Aim: To provide descriptive data regarding the medications being prescribed to patients who have a life-limiting illness at the time of referral to a palliative care service in regional Australia, with particular focus on lipid-lowering medications.

Methods: A prospective case note review of 203 patients reporting the number of medications prescribed and, for lipid-lowering medications, the indication and level of prevention sought (primary, secondary, tertiary). Rates were compared by performance status, disease phase and comorbidity burden.

Results: Mean number of regular medications prescribed was 7.2, with higher rates observed in those patients with a non-malignant primary diagnosis (rate ratio 1.28, confidence interval (CI) 1.11–1.50) or poorer performance status (rate ratio 1.37, CI 1.11–1.69) and lower rates for those in the terminal phase of disease (rate ratio 0.48, CI 0.30–0.76). Over one fifth of patients were prescribed a lipid-lowering medication, and two fifths of these prescriptions were for primary prevention of cardiovascular disease. Patients in the highest quartile of Charlson Comorbidity Index score were 4.6 (CI 2.06–10.09) times more likely to be prescribed a lipid-lowering medication than those in the lowest quartile.

Conclusions: Polypharmacy is prevalent for this group of patients, placing them at high risk of drug-drug and drug-host interactions. Prescribing may be driven by risk factors and disease guidelines rather than a rational, patient-centred approach.
Introduction

Background

All medications have risks and side-effects, but the population of patients with life-limiting disease receiving palliative care is particularly susceptible to adverse effects. As death approaches, drug pharmacokinetics and pharmacodynamics change because of altered metabolism, organ dysfunction and weight loss, while potential for benefit is likely to lessen over time. Therefore, the balance of benefit versus burden of ongoing treatments for comorbid disease in palliative populations needs careful and ongoing consideration as the life-limiting illness progresses.

There is a growing body of literature regarding the use of preventative medications among patients with life-limiting illnesses. Two studies have found that approximately one fifth of patients with advanced cancer are prescribed one or more medications considered unnecessary. There is also evidence that prescriptions increase towards the end of life. A previous Australian prospective cohort study of 260 patients found the total number of medications prescribed increased by 1.49 medications within the month prior to death from a baseline mean of 4.9 at referral to a palliative care service. This change was due to an increase in symptom-specific medications, modulated by only a small decrease in medications for comorbid medical conditions.

Lipid-lowering medications

In Australia, in 2009–2010, approximately 20% of adult general practice patients were being prescribed a statin. Lipid-lowering medications made up 4.4% of total prescribing. Statin use in Australia is higher than in Europe and still rising. There is debate regarding the discontinuation of such medications when prognosis is limited, but there are currently limited data on prescribing rates among palliative populations. An American study found that 52% of patients with recognisable life-limiting illness were prescribed a statin within 6 months of death, and another found that of those patients who were prescribed a statin at the time of diagnosis of advanced lung cancer, only 53% had the statin discontinued before death. A recent longitudinal study of 539 patients receiving statins at diagnosis of poor prognosis cancer showed no significant difference in timing of statin discontinuation or cardiovascular mortality in those taking the statin for primary versus secondary prevention.

These trends are concerning given what is known about the number needed to treat and, importantly, over what timeframe outcomes for lipid-lowering medications are likely to be achieved. Randomised, controlled trials have found that treating 100 patients for 5 years with a statin prevents approximately five major cardiovascular events and one stroke. Risk reduction is more immediate in the acute coronary syndrome setting where treating 100 patients prevents approximately one major cardiovascular event per month. Number needed to harm is also an important factor with up to 8% of patients experiencing nausea, vomiting or abdominal pain, up to 7% mild myalgias and, very rarely, rhabdomyolysis. Statin-induced muscle damage is a particularly pertinent issue in the palliative population who often become progressively cachectic and weak as a result of their primary disease.

This prospective study aims to provide descriptive data regarding the number of, type of and indications for medications being prescribed for a consecutive cohort of patients who have a life-limiting illness at the time of referral to a palliative care service, with particular focus on lipid-lowering medications. Its significance is in providing unique data that will contribute to a growing body of literature around the use of medications for comorbid illnesses in patients who are terminally ill.

Methods

Study setting

Palliative care services in Victoria, Australia are funded regionally by the state government to provide inpatient, outpatient and consultative advice delivered by specialist nurses, physicians and allied health staff. Referral triggers may include symptom control, psychosocial support and care coordination. Early referral, while continuing to treat the life-limiting illness in parallel with symptom control, is increasingly common, and as such, patients may be actively undergoing disease-modifying therapies while enrolled in a palliative care service.

The Grampians Regional Palliative Care Team and Ballarat Hospice Care Incorporated are two specialist medical, nursing and allied health teams that work together to provide regional consultative palliative care services to 224 000 people with diverse socioeconomic and cultural backgrounds, living in a 48 000-km² region in western Victoria.

Study participants

A prospective, consecutive case note review was performed of 203 patients newly referred to these services.
from August 2011 for 6 months. Inclusion criteria were age of 18 years or more, and diagnosis of an incurable, life-limiting illness. Both inpatient hospital and outpatient community records were used depending on the location of the patient at first clinical contact.

**Data collection**

Age, gender, primary diagnosis, comorbid diagnoses and a complete medication list were recorded for each patient at the time of first clinical contact with the palliative care service prior to any changes instituted during that contact. All data were de-identified. Chemotherapy agents were not included unless they were regular oral medications being administered at the time of review. Over-the-counter and non-prescribed therapies were not included. Functional status was measured by the Australian Modified Karnofsky Performance Scale (AKPS), an 11-level ordinal scale wherein 100 is normal with no signs of disease and zero is deceased. Place in disease trajectory was documented by the relative values, categorical Palliative Care Outcomes Collaboration (PCOC) phase – stable, unstable, deteriorating and terminal. Charlson Comorbidity Index was used to measure total burden of comorbidity where higher scores indicate greater illness burden. Number of days between first clinical contact and death, loss to follow up or end of the study period were also noted.

**Analysis**

Prescriptions were grouped into regular medications with the subset of lipid-lowering agents specifically coded and pro re nata (as required) medications (pro re nata prescriptions are discussed in a separate paper). The prescribing intent for each regular prescription was classified as being for treatment of comorbid disease or for symptom control. The prescribing indication for each lipid-lowering medication was established by review of diagnoses. Where necessary, this was clarified by contacting the treating physician, including the patient’s general practitioner. Each medication/indication pair was then coded according to the prevention strategy of the prescription (Table 1). ‘Primary prevention’ was coded if there was laboratory evidence of hyperlipidaemia or other cardiovascular risk factors without documented cardiovascular disease. ‘Secondary prevention’ was coded if there was symptomatic evidence of angina, limb claudication or ‘ischaemic heart disease’ but no documented irreversible end-organ damage. ‘Tertiary prevention’ was coded when the patient had a documented cardiovascular event, such as previous myocardial infarction, stroke, arterial stent or limb amputation with irreversible pathology. If there were multiple coexisting indications for one drug, the indication implying the highest level of prevention was used.

Data were entered into Microsoft Office Excel version 14.3.1 (2011; Redmond, WA, USA), and statistical analysis was performed using Stata version 12.1 (Stata Corp., College Station, TX, USA). Because of over dispersion of data, prescribing of regular medications was analysed using the negative binomial model. Prescribing of lipid-lowering agents was analysed using Fisher’s exact test and a log-binomial model for relative risk.

**Ethics and reporting**

Ethics approval was granted by the Ballarat Health Services Human Research Ethics Committee. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) consensus guidelines for observational studies.

**Results**

**Population characteristics**

Two hundred and three consecutive patients were included in the study. The mean age was 73, and 59% were male. (Table 2) Over two-thirds (68%) had a malignancy as their primary life-limiting illness compared with 79% of patients referred to palliative services nationally.

**Prescriptions for regular medications**

The mean number of regular medications each patient referred to palliative care services was prescribed was 7.2

<table>
<thead>
<tr>
<th>Prevention level</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Risk factor(s) present without documented disease</td>
<td>Hyperlipidaemia</td>
</tr>
<tr>
<td>Secondary</td>
<td>Documented evidence of disease without irreversible end-organ damage</td>
<td>Angina or limb claudication</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Documented irreversible end-organ damage</td>
<td>Myocardial infarction, stroke, arterial stent insertion, limb amputation</td>
</tr>
</tbody>
</table>
The majority of medications prescribed was for the treatment of comorbid disease (mean 5.3 ± 3.5) rather than for symptom control (mean 1.9 ± 2.0), and this ratio did not significantly differ by disease phase or performance status. Higher numbers of medications were observed in those patients with non-malignant compared with malignant primary diagnoses (8.5 vs 6.6, rate ratio 1.28, CI 1.11–1.50) and with poorer performance status (mean 7.7 in AKPS 0–40 vs 5.6 in AKPS 80–100; rate ratio 1.37, CI 1.11–1.69; Fig. 1). Patients in the terminal phase of their disease (those in the last few hours or days of life who are typically unable to swallow tablets) were prescribed less than half the number of regular medications than those in any other disease phase (rate ratio 0.48, CI 0.30–0.76; Fig. 2). Variation in Charlson Comorbidity Index score was not associated with any significant difference in the number of medications palliative patients

### Table 2. Population characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean ± SD</td>
<td>72.9 ± 12.6</td>
</tr>
<tr>
<td>Median</td>
<td>75</td>
</tr>
<tr>
<td>Range</td>
<td>37–98</td>
</tr>
<tr>
<td>Male sex NA</td>
<td>NA</td>
</tr>
<tr>
<td>Died NA</td>
<td>119 (58.6)</td>
</tr>
<tr>
<td>Admission to death (days) Mean</td>
<td>92.9</td>
</tr>
<tr>
<td>Range</td>
<td>0–424</td>
</tr>
<tr>
<td>Censored NA</td>
<td>NA</td>
</tr>
<tr>
<td>Alive at 16 November 2012 NA</td>
<td>NA</td>
</tr>
<tr>
<td>Lost to follow up NA</td>
<td>NA</td>
</tr>
<tr>
<td>Admission to censor (days) Mean</td>
<td>220.2</td>
</tr>
<tr>
<td>Range</td>
<td>0–452</td>
</tr>
<tr>
<td>Primary disease NA</td>
<td>NA</td>
</tr>
<tr>
<td>Malignant NA</td>
<td>138 (68.0)</td>
</tr>
<tr>
<td>Colon NA</td>
<td>25 (12.3)</td>
</tr>
<tr>
<td>Lung NA</td>
<td>22 (10.8)</td>
</tr>
<tr>
<td>Upper GI NA</td>
<td>19 (9.4)</td>
</tr>
<tr>
<td>Prostate NA</td>
<td>19 (9.4)</td>
</tr>
<tr>
<td>Haematological NA</td>
<td>13 (6.4)</td>
</tr>
<tr>
<td>Breast NA</td>
<td>8 (3.9)</td>
</tr>
<tr>
<td>Gynaecological NA</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>CNS NA</td>
<td>4 (1.97)</td>
</tr>
<tr>
<td>Other NA</td>
<td>24 (11.8)</td>
</tr>
<tr>
<td>Non-malignant NA</td>
<td>NA</td>
</tr>
<tr>
<td>Respiratory failure NA</td>
<td>20 (9.85)</td>
</tr>
<tr>
<td>Cardiac failure NA</td>
<td>10 (4.9)</td>
</tr>
<tr>
<td>Renal failure NA</td>
<td>7 (3.5)</td>
</tr>
<tr>
<td>Neurodegenerative NA</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Hepatic failure NA</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Other NA</td>
<td>19 (9.4)</td>
</tr>
<tr>
<td>AKPS Mean ± SD</td>
<td>48.2 ± 19.1</td>
</tr>
<tr>
<td>Median</td>
<td>50</td>
</tr>
<tr>
<td>Range</td>
<td>10–90</td>
</tr>
<tr>
<td>AKPS ≥80 NA</td>
<td>NA</td>
</tr>
<tr>
<td>AKPS 50–70 NA</td>
<td>NA</td>
</tr>
<tr>
<td>AKPS ≤40 NA</td>
<td>NA</td>
</tr>
<tr>
<td>PCOC Phase 1 (stable) NA</td>
<td>NA</td>
</tr>
<tr>
<td>PCOC Phase 2 (unstable) NA</td>
<td>NA</td>
</tr>
<tr>
<td>PCOC Phase 3 (deteriorating) NA</td>
<td>NA</td>
</tr>
<tr>
<td>PCOC Phase 4 (terminal) NA</td>
<td>NA</td>
</tr>
<tr>
<td>Charlson Comorbidity Index Mean ± SD</td>
<td>8.4 ± 2.8</td>
</tr>
<tr>
<td>Median</td>
<td>8.0</td>
</tr>
<tr>
<td>Range</td>
<td>2–20</td>
</tr>
</tbody>
</table>

AKPS, Australian-Modified Karnofsky Performance Status; CNS, central nervous system; GI, gastrointestinal; NA, not applicable; PCOC, Palliative Care Outcomes Collaborative; SD, standard deviation.
were prescribed when compared by quartiles; similarly, no association for survival was identified when those patients who died within 1 week following admission were compared with those who survived longer.

**Prescriptions for lipid-lowering medications**

Forty-four (21.7%) patients were prescribed one or more lipid-lowering medications upon referral to palliative care, with 46 prescriptions in total. Two fifths (40.5%) of these prescriptions were for primary prevention of cardiovascular disease, 2.4% for secondary prevention and 57.1% for tertiary prevention. Forty-three (93.5%) of these prescriptions were for statins. There was no significant difference in rates of prescribing in those patients with a malignant compared with non-malignant primary diagnosis (23.2% vs 18.5%), nor with varying performance status (20.7% in AKPS 0–40 vs 16.7% in AKPS 80–100). No patients in the terminal phase of disease were prescribed a lipid-lowering medication when they were referred to palliative care compared with 44 of 187 (23.5%) patients who were in other disease phases ($P = 0.026$; Fig. 3). Survival beyond the first week after admission was associated with a significantly higher likelihood of being prescribed a lipid-lowering medication at the time of presentation to palliative care services (24.6% vs 6.5%, $P = 0.03$); similarly, patients in the highest quartile of Charlson Comorbidity Index (scores of 11–20) were 4.6 times more likely to be prescribed a lipid-lowering medication than those in the lowest quartile (scores of 2–7; CI 2.06–10.09; Fig. 4).

**Discussion**

This study confirms that people with advanced life-limiting illnesses referred to palliative care are being
prescribed with many medicines; with an average of more than seven medications per patient, polypharmacy is highly prevalent.

The numbers of medications prescribed are even higher than previous reports and present many potential concerns. First, the risk of an adverse drug interaction exceeds 80% when more than seven medications are taken together, which was the case for one half of the studied population at time of referral to the palliative care service. Adverse drug events may be wrongly attributed to disease progression or global deterioration, triggering a cascade of prescribing – adding new medications to counter the perceived unwanted effects of other medications. Second, many medications are prescribed as more than once daily dosing with multiple tablets per dose depending on the formulations available. Although data regarding dosing and number of tablets were not collected, the mean of 7.2 medications represents an even higher pill burden than the simple number of medications might suggest. Difficulties with appetite, early satiety and constipation are frequently encountered in this population; nutrition cannot be derived from pills, and pill volume may limit other oral intake.

Doctors typically prescribe individual medications in accordance with individual disease-specific guidelines. Patients experience this as polypharmacy with interventions for each disease independently. It is therefore not surprising that in this review, clinicians prescribed more medications for treatment of comorbid disease than symptom control and for those patients with a non-malignant primary diagnosis than those with a malignant primary diagnosis, although it must be noted that this study did not include the prescription of chemotherapy agents other than those prescribed on a regular oral basis (thus, the chemotherapy burden is largely invisible). There was no significant difference in prescribing with variations in Charlson Comorbidity Index, suggesting that prescribing may be driven by risk factors more so than diagnosed diseases.

Clinicians also prescribed more medications in the setting of poorer performance status, possibly representing an attempt to slow or reverse the advance of symptomatic disease or treat symptoms. The number of medications prescribed did fall in the terminal phase of disease, wherein typical features include drowsiness and difficulty swallowing. Hence, this reduction in medications may merely be a response to the patient’s inability to ingest the tablet physically rather than a truly proactive review and rationalisation of prescribing by the treating clinician based on the initial intent of each prescription. This hypothesis is supported by the observation that prescribing rates were not significantly different for those patients who died within 1 week from referral compared with those who survived longer or that the ratio of medications prescribed regularly for treatment of comorbid disease to those for symptom control did not significantly differ across disease phase or AKPS.

The proportion of patients who were prescribed lipid-lowering medications in this study was lower than reported in a previous retrospective cohort study of patients in the last 6 months of life, although the current cohort also had a shorter survival time with a mean of 92.9 days following referral. Two fifths of lipid-lowering medications prescribed were for primary prevention, which is of negligible benefit in the setting of life-limiting illness given the very high number needed to treat and prolonged time to benefit at a population level. This means that 18 patients were likely only exposed to the harms of lipid-lowering medications. Even secondary and tertiary prevention in palliative populations is of arguable benefit as death approaches, despite evidence of slightly increased risk of an acute coronary syndrome upon withdrawal of statins. While statins do appear to have immediate non-lipid-mediated anti-inflammatory effects, this may be clinically significant only in the acute infarction period and must be weighed against the potential for drug-host and drug-drug interactions, and adverse effects such as myalgias and gastrointestinal upset that may worsen quality of life, may cause irreversible deterioration, or contribute to a ‘cascade of prescribing’.22

Primary diagnosis did not alter prescribing rates, but patients with higher Charlson Comorbidity Index scores were prescribed significantly more lipid-lowering medications. This is not a surprising finding given that dyslipidaemia is a common risk factor for many diseases that are assessed within the Charlson Comorbidity Index, including myocardial infarction, cerebrovascular disease and peripheral vascular disease. The lack of reduction in prescribing rates for those patients who died within a week of referral compared with those who survived beyond indicates either a lack of consideration of benefit over time versus burden of therapy, or poor prognostication. Previous prospective research has found physicians overestimate prognosis in terminally ill patients at the time of referral to a palliative care service by up to a factor of five. Worryingly, poor performance status did not trigger a reduction in prescribing among these patients either despite the almost universal irreversibility of decline in function at this time as well as concerns of clinical futility and potential for drug interactions and adverse drug effects that may contribute (potentially unrecognised) to clinical deterioration.

Cessation of medications prescribed on a long-term or life-long basis for comorbid illness may pose challenges to the clinician–patient relationship. The patient may feel abandoned or perceive medical advice as inconsist-
ent, thereby eroding trust in the clinician. Medication cessation may also precipitate further confrontation with mortality and result in distress.1 These concerns are not a justification for inappropriate prescribing but do highlight the need for all management decisions to be communicated with empathy that balances with reality.26

Limitations of this study include the method of data collection from case note review supplemented by clarification of indications for medications, when needed, from treating physicians. Medical histories were sometimes incomplete, and the treating physician did not always know why a particular medication had been commenced, although they continued to prescribe it, a concern in itself. This disturbing practice of uninformed prescribing means that the level of prevention strategy may have been underestimated in some instances and overestimated in other cases. Medications prescribed may not all be dispensed or taken, so these data likely overestimate the actual number of medications taken by this population. However, as the subject of this paper is rational prescribing, the physician’s prescription is the appropriate level of prescribing to scrutinise.

Because of the expected skewed nature of some variables at time of referral to a palliative care service reflecting clinical referral triggers, some subgroups were small (e.g. only 12 patients with an AKPS of 80+ and 16 patients in the terminal phase of disease). The population described is reasonably similar to national PCOC data,19 and descriptive information regarding the setting and population has been included to improve generalisability.27

This study has shown that the volume of prescribing for comorbid illness in the setting of life-limiting disease is high and does not always reduce in response to clinical deterioration where little clinical benefit is possible or theoretically likely. Lipid-lowering medications in particular are frequently prescribed for poorly described indications with unfavourable risk to benefit ratios. These findings provide the impetus for a shift towards more conscious, informed and rational prescribing in palliative populations. Various frameworks have been previously described, taking into account the characteristics of the illness and medication, the prescribing intent, and the risk analysis.1,28–30

This current study adds to the growing body of knowledge to inform the complex decision-making process of medication reduction, cessation or substitution towards the end of life. Further research is warranted to investigate the potential benefit of pharmacist reviews, as well as the optimal timing for medication changes. Given the variable patterns of care in referral-based palliative care, longitudinal prospective data from several services are required to understand more fully the nature, magnitude, risks and benefits of prescribing in the setting of life-limiting disease.

Conclusions

This prospective study provides key baseline data documenting high rates of regularly prescribed medications – in particular of lipid-lowering medications – among a palliative population in regional Australia. Polypharmacy is common, carries risk and is not always reduced in response to clinical deterioration when the rationale for prescribing may become less convincing.

When prescribing any medication in the palliative setting, clinicians should carefully weigh the benefits likely to be realised within the timeframe of the patient’s prognosis against the potential burdens that may be physical, psychological, financial or social.

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References

Inpatient antibiotic consumption in a regional secondary hospital in New Zealand

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Key words
antibacterial agents/therapeutic use, secondary care/statistics and numerical data, pharmacy service, New Zealand, drug resistance.

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Abstract

Background: Reporting of antibiotic consumption in hospitals is a crucial component of antibiotic stewardship, but data from Australasian secondary hospitals are scarce. The hypothesis of this audit is that antibiotic consumption in secondary hospitals would be lower than in tertiary centres.

Aims: The study aims to present the first published audit of antibiotic consumption from a secondary hospital in New Zealand compared with two tertiary centres.

Methods: Hospital population-level data were retrospectively accessed to identify all systemic antibiotics dispensed to adult inpatients at Taranaki District Health Board during 2011. Consumption was calculated in defined daily doses per 100 inpatient-days and per 100 admissions, stratified by drug class. Comparison was against published data from two tertiary centres.

Results: Total consumption was lower, but that of high-risk antibiotic classes was higher than both tertiary centres. The relative consumption of lincosamides was 4.0 and 2.6 times higher than the two tertiary centres, with an associated 14% incidence of *Clostridium difficile* associated diarrhoea within 3 months.

Conclusion: Our secondary hospital appears to consume the wrong types of antibiotic rather than too much. Data from all Australasian hospitals, stratified by clinical service area and hospital level, are required for clinically relevant benchmarking.

Introduction

Excessive consumption of antibiotics in hospitals is strongly associated with higher incidence of antibiotic-resistant organisms\(^1\)\(^-\)\(^6\) and *Clostridium difficile*-associated diarrhoea (CDAD).\(^7\)\(^-\)\(^8\) Antibiotic stewardship programmes to improve antibiotic prescribing in hospitals have been shown to reduce antibiotic resistance,\(^9\)-\(^11\) incidence of CDAD\(^12\)-\(^14\) and costs\(^15\) while improving clinical outcomes.\(^16\)

Monitoring and reporting antibiotic consumption in hospitals is a core aspect of any antibiotic stewardship programme and is promoted by the World Health Organisation (WHO)\(^17\) and the United States Centers for Disease Control and Prevention.\(^18\) Most institutions use aggregate population-level data, expressing consumption using WHO-defined units adjusted by hospital demographic figures,\(^19\) and using standardised reporting methods.\(^20\)-\(^21\) This enables benchmarking between institutions,\(^22\) a process made more clinically relevant when data are stratified to the hospital level and/or specialty.\(^23\)-\(^24\)

In Europe, 34 countries participate in national-level antibiotic consumption surveillance,\(^25\) but this is not stratified by hospital nor specialty. A multicentre surveillance programme in France provides stratification by service and hospital type.\(^24\) This demonstrated that consumption was higher in teaching than in non-teaching hospitals. A sample of 40 non-university regional general hospitals in Germany concluded that patient care area was a better predictor of consumption than hospital size.\(^26\) National surveillance in Australia\(^27\) currently has incomplete participation, few secondary hospitals participate, and the data are not yet stratified by hospital size. In New Zealand only two tertiary institutions – Auckland,\(^28\) and Capital and Coast\(^29\) District Health Boards (DHB) – have published their antibiotic consumption to date.

Health services in New Zealand are provided by 20 DHB. Fourteen of these provide only secondary-level services to their catchment population, while the other six also provide tertiary-level services to other DHB.\(^30\) The secondary DHB serves 45% of New Zealand’s population\(^31\) and accounts for 38% of case weight-adjusted inpatient service delivery.\(^32\)

Funding: C. Hopkins was awarded a cash prize by the Department of Medicine, Taranaki DHB for this project.

Conflict of interest: C. Hopkins was employed by Taranaki DHB at the time of completion of this audit.

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Taranaki DHB (TDHB) is a secondary DHB in a provincial region of New Zealand’s North Island, serving a population of 109,800 with a high proportion of rural residents. It contains 235 beds in two hospitals: a base hospital in the main urban centre and a small rural hospital. No inpatient haematology, oncology or transplant service is provided, although outpatients under these services are sometimes admitted under general teams. The Intensive Care Unit also carries out high dependency and coronary care functions. There is no formal antibiotic stewardship programme nor a resident clinical microbiologist or infectious diseases physician.

Presented here is the first published antibiotic consumption audit from a secondary DHB in New Zealand, benchmarked against two tertiary DHB. Due to the less complex casemix at secondary hospitals, a lower consumption of total and broad-spectrum antibiotics at TDHB is hypothesised.

Methods

The methodology was based as much as possible on published guidance and publications from two other New Zealand DHB.

Data were obtained retrospectively from computerised pharmacy databases. All adult inpatients were included between 1 January and 31 December 2011. All oral and parenteral antibiotics were analysed using WHO-defined drug classifications and defined daily doses (DDD). Inpatient-days (defined as one occupied bed at midnight) and admissions data were obtained from TDHB Business Unit; population data were obtained from NZ Statistics. Consumption was calculated in DDD/100 inpatient-days, DDD/100 admissions and DDD/1000 inhabitants/day. Data were stratified by antibiotic class, inpatient unit and month.

Paediatric, outpatient and operating theatres prescribing was excluded. The maternity unit at the main base hospital was included, but the smaller rural maternity unit was excluded.

Lincosamide consumption was unexpectedly high. Individual electronic clinical records were therefore accessed to verify the quantity consumed. Additional data on treating specialty, mortality, new onset of CDAD within 3 months and beta-lactam allergy status were collected.

Prospective approval to carry out this audit was given by the Head of Department of Medicine at Taranaki Base Hospital. Formal ethics committee approval was not considered necessary. Submission for publication in a peer-reviewed journal was approved by the Chief Medical Advisor of TDHB (G. Simmons, pers. comm., 2012). The audit was presented at the TDHB Hospital Grand Round on 1 November 2012.

Results

There was a total of 14,315 admissions and 50,243 inpatient-days in 2011, giving a mean length of stay of 3.51 days.

Total consumption (Table 1) at TDHB was lower than at both of the tertiary New Zealand DHB. Consumption at TDHB was higher than mean consumption in samples of secondary hospitals in Germany and France but lower than a mixed sample of secondary and tertiary hospitals in Australia. There was no significant seasonal difference in antibiotic consumption (data not shown).

The inpatient unit in our rural hospital had the highest consumption of all inpatient units (117.6 DDD/100 inpatient-days compared with 106.9 on the intensive care unit).

The most consumed classes at TDHB in 2011 were penicillins combined with beta-lactamase inhibitors (predominantly amoxicillin-clavulanate), macrolides (e.g. roxithromycin, erythromycin) and second-generation cephalosporins (predominantly cefuroxime). The full list is shown in Table 2.

TDHB’s antibiotic consumption by class is benchmarked against ADHB and CCDHB in Figure 1. There is considerable variability between the three DHB.

Table 1 Total antibiotic consumption at three New Zealand District Health Boards and three international multicentre surveys

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DDD per 100 inpatient-days</td>
<td>65.8</td>
<td>80.3</td>
<td>78.5</td>
<td>49.4</td>
<td>37.2</td>
<td>96.9</td>
</tr>
<tr>
<td>DDD per 100 admissions</td>
<td>230.8</td>
<td>312.4</td>
<td>356.4</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>DDD per 1000 inhabitants/day</td>
<td>0.83</td>
<td>1.91</td>
<td>1.32</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Germany, secondary indicates weighted mean data from 17 non-university regional hospitals, containing between 200 and 399 beds, in South-West Germany. France, secondary indicates mean data from 165 non-teaching public hospitals in France. Audit year is indicated in parentheses. Australia, mixed indicates mean data from 34 hospitals of various sizes and levels in Australia between July 2010 and June 2011. ADHB, Auckland District Health Board; CCDHB, Capital and Coast District Health Board; DDD, defined daily doses; N/A, not applicable; TDHB, Taranaki District Health Board.
Comparing TDHB with both of the tertiary DHB, the largest absolute differences are seen with macrolides (higher consumption at TDHB), beta-lactamase resistant penicillins and extended-spectrum penicillins (lower consumption at TDHB).

The largest relative difference in consumption was seen with lincosamides (clindamycin and lincomycin), with higher consumption at TDHB by a factor of 4.0 compared with ADHB and 2.6 compared with CCDHB. The next two classes with the highest relative consumption at TDHB compared with both tertiary DHB were macrolides and third-generation cephalosporins (ceftiraxone, cefazidime and cefotaxime). The two classes with the lowest relative consumption against both tertiary DHB were aminoglycosides (e.g. gentamicin, tobramycin) and carbapenems (e.g. meropenem, imipenem).

Of 105 patients prescribed a lincosamide in the 12-month audit period, 15 (14%) developed an in-hospital diagnosis of CDAD within the next 3 months. Thirty-seven (35%) had a documented allergy to beta-lactam agents, which is the most common indication for lincosamides. Lincosamide consumption at TDHB (3.2 DDD/100 inpatient-days) was higher than all 34 hospitals in the sample from Australia (2.5 DDD/100 inpatient-days). 27

Lincosamides, glycopeptides, carbapenems, fluoroquinolones, and third- and fourth-generation cephalosporins are considered to be ‘high-risk’ classes and priorities for restriction. The combined absolute consumption (in DDD/100 inpatient-days) of these ‘high-risk’ classes was higher at TDHB (12.4) than at both ADHB (8.5) and CCDHB (11.1).

### Discussion

This audit presents the first published antibiotic consumption data from a secondary DHB in New Zealand, benchmarked against two tertiary DHB.

The hypothesis that TDHB would consume less total antibiotics than the tertiary DHB was proven to be true. However, this hypothesis was not true across all antibiotic classes.

The most striking result from this audit was that of excess consumption of lincosamides at TDHB by a factor of 2.6- to 4-fold compared with ADHB and CCDHB, and higher than all 34 Australian hospitals participating in national surveillance. The 14% incidence of CDAD among inpatients administered lincosamides is concerning because clindamycin has previously been identified as a high-risk agent for CDAD. 33

The combined absolute consumption of high-risk classes was higher than at both of the tertiary DHB. This is both unexpected and concerning, considering the differences in casemix. So TDHB appears to be using the wrong antibiotics rather than too much.

A further concern is that total consumption at TDHB exceeded that in a sample mean from comparable hospitals in Germany and France, the latter having been identified as one of the highest consumers of antibiotics in Europe. 24

The rural hospital inpatient unit had the highest consumption despite admitting only low acuity patients. Although data error may account for this unexpected finding, further audit is warranted.

The main limitation of this audit is the lack of peer data from Australasian secondary hospitals against which to compare. This necessitated benchmarking against two centres that differ greatly from TDHB in terms of size, casemix and infectious disease expertise. Additionally, this method did not analyse clinical

### Table 2: Total antibiotic consumption at Taranaki DHB in 2011 by antibiotic class

<table>
<thead>
<tr>
<th>Antimicrobial class (ATC code)</th>
<th>DDD/100 inpatient-days</th>
<th>DDD/100 admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclines (J01AA)</td>
<td>1.90</td>
<td>6.66</td>
</tr>
<tr>
<td>Penicillins with extended spectrum (J01CA)</td>
<td>4.44</td>
<td>15.58</td>
</tr>
<tr>
<td>Beta-lactamase-sensitive penicillins (J01CE)</td>
<td>0.63</td>
<td>2.20</td>
</tr>
<tr>
<td>Beta-lactamase-resistant penicillins (J01CF)</td>
<td>7.93</td>
<td>27.82</td>
</tr>
<tr>
<td>Penicillins with beta-lactamase inhibitors (J01CR)</td>
<td>10.45</td>
<td>36.68</td>
</tr>
<tr>
<td>First-generation cephalosporins (J01DB)</td>
<td>2.39</td>
<td>8.39</td>
</tr>
<tr>
<td>Second-generation cephalosporins (J01DC)</td>
<td>9.41</td>
<td>33.02</td>
</tr>
<tr>
<td>Third-generation cephalosporins (J01DD)</td>
<td>2.43</td>
<td>8.54</td>
</tr>
<tr>
<td>Fourth-generation cephalosporins (J01DE)</td>
<td>1.37</td>
<td>4.81</td>
</tr>
<tr>
<td>Monobactams (J01DF)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carbapenems (J01DH)</td>
<td>0.65</td>
<td>2.27</td>
</tr>
<tr>
<td>Trimethoprim (J01EA)</td>
<td>1.38</td>
<td>4.84</td>
</tr>
<tr>
<td>Sulphonamides (J01EC)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Trimethoprim with sulphonamides (J01EE)</td>
<td>1.28</td>
<td>4.50</td>
</tr>
<tr>
<td>Macrolides (J01FA)</td>
<td>10.14</td>
<td>35.61</td>
</tr>
<tr>
<td>Lincosamides (J01FF)</td>
<td>3.22</td>
<td>11.29</td>
</tr>
<tr>
<td>Aminoglycosides (J01GB)</td>
<td>0.70</td>
<td>2.45</td>
</tr>
<tr>
<td>Fluoroquinolones (J01MA)</td>
<td>3.84</td>
<td>13.47</td>
</tr>
<tr>
<td>Glycopeptides (J01XA)</td>
<td>0.83</td>
<td>2.91</td>
</tr>
<tr>
<td>Polymyxins (J01XB)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fusidic acid (J01XC)</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Imidazoles (J01XD)</td>
<td>2.39</td>
<td>8.39</td>
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<tr>
<td>Nitrofurans (J01XE)</td>
<td>0.38</td>
<td>1.34</td>
</tr>
<tr>
<td>Other agents (J01XX08)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All agents (J01)</td>
<td>65.75</td>
<td>230.78</td>
</tr>
</tbody>
</table>

ATC, anatomical therapeutic classification; DDD, defined daily doses; DHB, District Health Board.

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reasoning or appropriateness of the consumption. There are other limitations inherent in the method used; however, the use of a validated, standardised and internationally accepted methodology is the major strength of this audit.

Conclusion

Within these limitations, this audit demonstrates scope to improve antibiotic prescribing at TDHB and has prompted work to establish an antibiotic stewardship programme.

Antibiotic consumption and stewardship are crucial priorities in modern healthcare. This is equally as important in secondary hospitals, which serve almost half of New Zealanders, as in large tertiary centres. Yet there are no relevant data available to empower secondary hospitals to improve their antibiotic prescribing. This audit proves that it is possible to obtain this, with potentially important findings to be made. Antibiotic consumption surveillance is required in all hospitals in Australasia, stratified by size and level of hospital and by specialty, to supply relevant data to prescribing clinicians. This audit hopes to stimulate this process and to contribute to optimising antibiotic consumption.

Acknowledgements

I thank the following people for their assistance with completing this audit: Dr Campbell White (Taranaki DHB Physician and audit supervisor); Anna-Lee Innes (Taranaki DHB Pharmacy Technician); Dan Brotherton (Taranaki DHB Business Unit); Lisa Gilbert (Infection Control CNS, Taranaki DHB); and Mark Thomas (Infectious Diseases Physician, Auckland DHB).
Modification of the National Inpatient Medication Chart improves venous thromboembolism prophylaxis rates in high-risk medical patients

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Abstract

Background: Venous thromboembolism (VTE) is a significant contributor to morbidity and mortality in Australia. While there is well-established evidence for the use of VTE prophylaxis in hospital inpatients, adherence to such guidelines is poor.

Aim: The aim of the present study is to assess the impact of education and system change on improving rates of VTE prophylaxis in hospital inpatients.

Methods: We performed four consecutive audits of inpatient medical records of a regional hospital service over 2 years. The audits aimed to test the impact of serial interventions at increasing the appropriate use of VTE prophylaxis (based on risk assessment). The interventions were (i) staff education and (ii) a process change that mandated a prophylaxis decision by modifying the National Inpatient Medication Chart with ‘VTE avoidance’ preprinted in the first medication box.

Results: Our results from the baseline study showed that of the 236 medical inpatients reviewed, 80% were at high risk of VTE. Of this high-risk cohort, 34.9% (confidence interval (CI) 28–42%) had appropriate prophylaxis decisions. Post the education intervention, 43.2% (CI 37–49%) of the high-risk cohort received appropriate VTE prophylaxis, an improvement of 8.3% (CI −1% to 18%) from baseline. With the subsequent introduction of a process change, 82.1% (CI 66–92%) of the high-risk cohort received appropriate prophylaxis, an improvement of 47.2% and 38.8% (CI 24–54%) when compared with baseline and education respectively. Retention rates at 11 months postsystem change were 73% (CI 55–86%).

Conclusions: This study therefore concluded that while education has an impact on rates of appropriate VTE prophylaxis, it is system change that has the most marked and sustained effect.

Introduction

Venous thromboembolism (VTE) is a common cause of preventable morbidity, mortality and healthcare utilisation.1,2 In 2008 in Australia, there was an estimated 14 716 cases of symptomatic VTE, of which 5285 resulted in mortality.1 This represents an incidence of 0.74 per 1000 population per year, 7% of all deaths in Australian hospitals, and a cost to the community of 1.72 billion.3

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Key words
venous thromboembolism, evidence-based practice, prophylaxis, enoxaparin, education.

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effective at reducing the incidence of disease.\textsuperscript{1,2} In fact, studies have shown that thromboprophylaxis in high-risk medical inpatients can reduce the risk of VTE by 63%.\textsuperscript{4} Measures to improve VTE prevention are recommended, and this is reflected in Australian and International Guidelines.\textsuperscript{2,5} However, despite these recommendations, recent studies have demonstrated that VTE prophylaxis in medical patients at risk remains under-utilised.\textsuperscript{6} The Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) study reported that 51.8\% of hospital inpatients were at risk of VTE, but only 39.5\% of at risk medical patients and 58.5\% of at risk surgical patients received appropriate prophylaxis.\textsuperscript{6}

There have been suggestions on how to bridge this gap between evidence and practice, with particular focus on guideline, policy and education.\textsuperscript{7} Studies addressing this have suggested that education has a marginal effect and that sustainable improvement requires a multifaceted approach that may include audit-feedback and process change.\textsuperscript{8} This paper describes sequential attempts to improve appropriate VTE prophylaxis and the differential rates of uptake. It demonstrates the importance of a multifactorial approach including process change on improving rates of appropriate VTE prophylaxis.

The aim of this study is to assess the impact of education and system change on improving rates of appropriate VTE prophylaxis.

### Methods

Over 1 month, a prospective bedside and chart assessment was performed on all medical patients with an admission duration of greater than 3 days. Patients at high risk of VTE were identified (Table 1), and the number for whom an appropriate prophylaxis decision was made was noted. An appropriate prophylaxis decision would be the one consistent with the published guidelines including no prophylaxis in high-risk patients where contraindications exist.\textsuperscript{3}

Following the baseline audit, a specialist nurse was employed to educate nursing and medical staff regarding VTE risk and the use of prophylaxis. Guidance was in accordance with the Australian and New Zealand Working Party on the Prevention of Venous Thromboembolism.\textsuperscript{5} Education was delivered over a 4-month period through intern training, providing feedback to nurses, and at least two in-service presentations per ward. A 1-month prospective audit was performed 2 months posteducation intervention (Fig. 1). Medical records of medical inpatients were reviewed using the earlier criteria to identify the number of patients at risk and the appropriateness of the prophylaxis decision made.

Six months following the education intervention, the process change was instigated. The process change mandated a prophylaxis decision by modifying the National

### Table 1 Recommended prophylaxis in acute medical illness\textsuperscript{4}

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Clinical features</th>
<th>Recommended prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Age &gt;60 years\textsuperscript{†}</td>
<td>LDUH or LMWH or GCS and/or IPC if heparin is contraindicated</td>
</tr>
<tr>
<td></td>
<td>Ischaemic stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of VTE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decompensated cardiac failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Active cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute on chronic lung disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute on chronic inflammatory disease</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{†}While patients aged over 60 years are currently classified as high risk, those that are otherwise well and ambulant may not be at high risk for VTE in the absence of other risk factors. GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LDUH, low dose unfractionated heparin; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.
Results

Inpatient Medication Chart (NIMC) with ‘VTE avoidance’ preprinted in the indication space of the first medication box (Fig. 2). Three months after this modification, the pharmacy department conducted a point prevalence audit of all ward medication charts with the aim of determining (i) patient risk of VTE, (ii) whether a prophylaxis decision had been made, and (iii) whether the method of prophylaxis reflected guidelines. An identical audit was repeated 8 months later in order to examine retention rates (Fig. 1). No further educational work was undertaken post introduction of the process change.

Ethics approval for this project was obtained from St John of God and Ballarat Health Services Ethics Committee (Audit No – DIREC-L-04223).

In the initial baseline audit, 236 medical inpatient records were reviewed. Of these 236 patients, 80% were assessed to be at high risk of VTE. Of the 80%, 34.9% (confidence interval (CI) 28–42%) received either mechanical or pharmacological prophylaxis in accordance with guidelines.

Following the 4-month education programme, 300 cases were prospectively reviewed over a month. In this cohort, 83% of patients were at high risk of VTE, with 43.2% (CI 37–49%) receiving appropriate prophylaxis (Table 2). The introduction of an education programme altered VTE prophylaxis rates by 8.3% (CI –1% to 18%) (Fig. 3). While this was not statistically significant, it did show a positive trend.

Two months post process change (NIMC), the audit revealed that 90% of (n = 43) were at high risk of VTE, and 82.1% (CI 66–92%) received appropriate prophylaxis (Table 2). This demonstrates a 47.2% improvement from baseline and a 38.8% (CI 24–54%) improvement following cessation of the education programme (Fig. 3). Retention rates at 11 months following introduction of system change were 73% (CI 55–86%) (Table 2).
Discussion

In clinical practice, a gap between evidence and practice is commonly found. It has been reported that 30–45% of patients do not receive care in accordance with guidelines and a further 20–25% receive unnecessary or potentially harmful treatment. Adherence to VTE guidelines is particularly poor in medical inpatients where the rate of prophylaxis in high-risk patients appears to be 20% lower (39.5%) than in their surgical counterparts where it is better accepted.6 Our study was consistent with an evidence to practice gap, and we therefore aimed to increase the use of appropriate VTE prophylaxis.

Both education and system change have been proposed as effective approaches to clinical practice improvement, yet few studies have compared their relative efficacy. Birks et al. demonstrated that while education leads to moderate gains, the addition of system change vastly improved rates of VTE compliance. Similarly, our study showed that system change induced a dramatically higher rate of appropriate prophylaxis than education alone, with evidence of significant retention 11 months post the NIMC change. This confirms the impact of process change on long-term clinical practice.

Various studies have examined different methods of process change in VTE prophylaxis while producing similar results. Mitchell et al. used computer reminder systems, which improved rates of prophylaxis by 17.2%. The use of stickers and risk assessment tools on medication charts has also shown significant improvement in VTE prophylaxis rates. We chose an alteration to the NIMC as this would be simple to implement, require minimal education, and would integrate with usual clinical workflows by prompting a decision about VTE prophylaxis.

Our study suggests that education strategies are less effective than simple process changes in promoting appropriate use of VTE prophylaxis in medical inpatients. This is not to say education is not important, as it is the necessary first step in any change process. What we have demonstrated is that process change is an essential component in promoting sustainable change in practice, which is consistent with existing evidence.

Limitations

Although the results of this study have demonstrated the significant impact of process change, it is important to acknowledge that this work does have some limitations. This is a longitudinal study where the education intervention preceded the system change. There is thus the possibility of cross-over effects from education into the system change cohort. However, an educational programme that demonstrated a modest 8.3% improvement in practice at 2 months post intervention, subsequently causing a further 38% improvement in practice 6 months later, in the setting of frequently rotating junior medical staff, is unlikely. It is possible that the education primed the hospital staff for change and in doing so enabled the rapid introduction and acceptance of process change. Other issues relate to the known limitations of statistics calculated from non-random samples and the differing methods of data collection. While a 1-month prospective study was performed for the baseline and education

| Table 2 Effect of intervention (education and system change) on rates of VTE prophylaxis |
|----------------------------------------|----------------------------------------|-----------------|-----------------|-----------------|
|                                        | Baseline (preintervention)             | Post-education intervention | Post-NIMC change | 11 months post-NIMC change (retention) |
| No. reviewed cases                     | 236                                    | 300                          | 43               | 40               |
| High-risk cases                        | 180 (80%)                              | 249 (83%)                    | 39 (90%)         | 34 (85%)         |
| Prophylaxis given                      | 65 (34.9%)                             | 107 (43.2%)                  | 32 (82.1%)       | 25 (73%)         |
| (CI 28–42%)                            | (CI 37–49%)                            | (CI 60–92%)                  | (CI 55–86%)      |

CI, confidence interval; NIMC, National Inpatient Medication Chart; VTE, venous thromboembolism.
cohort, there was only a 1-day spot audit post system change and again at 11 months. This alteration of research method was necessary to embed the process in the health service’s ongoing quality system. Finally, our patients were risk stratified using the Australia and New Zealand Working Party guidelines. We acknowledge that there is no well-validated risk assessment tool for VTE and that other studies have shown both similar and lower proportions of patients considered as high risk for VTE.\textsuperscript{16–19} Given there is no clear consensus, we chose one guideline and applied it consistently throughout the study arms. Nonetheless, we assert that our conclusions regarding the superiority of system change do not depend on the acceptance of any one risk assessment tool.

References

Intravenous thrombolysis is unsafe in stroke due to infective endocarditis

W. J. Brownlee, N. E. Anderson and P. A. Barber

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Abstract

Embolic stroke is the most common neurological complication of infective endocarditis and a major source of morbidity and mortality. Septic embolism is considered a contraindication to intravenous thrombolysis in patients with ischaemic stroke because of concerns over an increased risk of intracranial haemorrhage. We describe a patient with occult endocarditis who was treated with thrombolysis for acute stroke and review other cases reported in the literature.

A 27-year-old woman presented following the sudden onset of dysphasia and right hemiparesis (National Institutes of Health Stroke Scale (NIHSS) score 15). She had been in good health with no relevant prior medical history until she collapsed at home. On admission, she was afebrile with no heart murmurs or peripheral embolic phenomena. Routine blood tests showed raised inflammatory markers with an erythrocyte sedimentation rate of 44 mm/h and C-reactive protein of 56 mg/L. A computed tomography (CT) brain scan showed loss of grey-white matter differentiation in the left insular cortex and hyperdensity in the M2/M3 branches of the left middle cerebral artery that were shown to be occluded on CT angiography. She was treated with intravenous tissue plasminogen activator (tPA) 0.9 mg/kg 2 h and 35 min after symptom onset. An hour later, she deteriorated with headache, drowsiness and worsening right-sided weakness (NIHSS score 20). Repeat CT brain scan showed no intracerebral haemorrhage (ICH). A magnetic resonance imaging brain scan 7 h and 35 min after symptom onset showed a 3-cm area of restricted diffusion in the left perisylvian/insular regions and additional areas of restricted diffusion in the right temporoparietal lobe, right superior parietal lobe and cerebellum (Fig. 1).

Review of the earlier CT brain scan and angiogram did not show involvement of these areas prior to treatment with tPA.

Later the same day, she became febrile. An urgent echocardiogram showed vegetations on the anterior leaflet of the mitral valve with mild-to-moderate mitral regurgitation. Blood cultures grew Streptococcus sanguis. She was treated with a 4-week course of intravenous penicillin, initially with gentamicin. Extensive dental work was undertaken for poor dentition. She was transferred to a rehabilitation facility and improved. Six months later, she was neurologically normal apart from minor right hand clumsiness.

Infective endocarditis (IE) remains an important clinical problem. There has been little change in the incidence of IE over the past 30 years with declining rates of rheumatic heart disease offset by increasing rates of IE among patients with prosthetic heart valves, intravenous drug use and elderly patients with degenerative valvular disease.1 Stroke due to cerebral embolism occurs in 10% of patients with IE and in half is the presenting problem.2 Risk factors for ischaemic stroke include Staphylococcus aureus infection, larger vegetation size and mitral valve position.2 Patients with IE are also at high risk of ICH because of septic and immune-complex-mediated arteritis, haemorrhagic transformation of infarcts, infiltration of meningeal vessels and rupture of mycotic aneurysms. Antiplatelet therapy is harmful in the primary prevention of embolic complications in patients with IE with an
excess of ICH, and thrombolysis for myocardial infarction, a much rarer embolic complication, has been associated with fatal ICH. Accordingly, patients with IE were excluded from registration trials of tPA for acute ischaemic stroke, and IE is listed as a contraindication to thrombolysis in most guidelines.

Seven patients with stroke due to IE treated with thrombolysis have now been reported (Table 1). The

Table 1 Patients treated with intravenous tPA for ischaemic stroke complicating infective endocarditis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Presentation</th>
<th>Baseline NIHSS</th>
<th>Time to tPA</th>
<th>Time to IE diagnosis</th>
<th>IE risk factors</th>
<th>Complications</th>
<th>Follow-up NIHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56/M</td>
<td>Right hemiparesis, dysphasia, HH</td>
<td>15</td>
<td>2 h, 36 min</td>
<td>48 h</td>
<td>None</td>
<td>None reported</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>46/M</td>
<td>Left hemiparesis</td>
<td>15</td>
<td>1 h, 50 min</td>
<td>&lt;6 h</td>
<td>IVDU</td>
<td>Multifocal parenchymal haemorrhage</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>65/F</td>
<td>Right hemiplegia, dysphasia, HH</td>
<td>21</td>
<td>2 h, 0 min</td>
<td>24 h</td>
<td>Immunosuppression</td>
<td>Multifocal parenchymal and subarachnoid haemorrhage</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>61/M</td>
<td>Right hemiparesis, dysphasia</td>
<td>21</td>
<td>1 h, 30 min</td>
<td>24 h</td>
<td>None</td>
<td>Multifocal parenchymal and subarachnoid haemorrhage</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>70/M</td>
<td>Right hemiparesis, dysphasia</td>
<td>13</td>
<td>2 h, 30 min</td>
<td>&lt;6 h</td>
<td>Occult malignancy</td>
<td>None reported</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>68/M</td>
<td>Right hemiparesis, dysphasia</td>
<td>12</td>
<td>2 h, 15 min</td>
<td>24 h</td>
<td>None</td>
<td>Multifocal parenchymal and subarachnoid haemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>27/F</td>
<td>Right hemiparesis, dysphasia</td>
<td>15</td>
<td>2 h, 20 min</td>
<td>&lt;6 h</td>
<td>Poor dentition</td>
<td>Early neurological deterioration not due to ICH</td>
<td>1</td>
</tr>
</tbody>
</table>

HH, homonymous hemianopia; ICH, intracranial haemorrhage; IE, infective endocarditis; IVDU, injecting drug use; NIHSS, National Institutes of Health Stroke Scale; NR, not reported; tPA, tissue plasminogen activator.
diagnosis of IE was made after the patient had been treated for the acute stroke in all cases. Our patient had no fever, heart murmur or embolic phenomena to suggest IE at presentation, although she did have raised inflammatory markers that were otherwise unexplained. Four of the seven reported patients had risk factors for IE including intravenous drug use, poor dentition, malignancy and immunosuppression. However, these may not be immediately obvious, for example, one patient was only found to have colorectal cancer after subsequent evaluation for weight loss and anaemia.7 The diagnosis of IE is often difficult with subtle manifestations that are easily overlooked when patients are being assessed for tPA.

Serious complications occurred in five IE patients treated with tPA. Four patients developed ICH,6,8 three of whom had no evidence of coagulopathy, hypertension or evidence of mycotic aneurysms on imaging studies.6 Our patient deteriorated with multifocal cerebral infarction following thrombolysis. In animal studies, treatment with streptokinase increased rates of systemic embolism despite more rapid resolution of vegetations.9 Fibrin is an important component of vegetations, and we speculate that tPA may have had a detrimental effect on the integrity of the mitral valve vegetations leading to further embolism.

Endovascular therapies with intra-arterial thrombolysis, with or without mechanical thrombectomy, may be an option for patients in whom tPA is contraindicated. Endovascular treatment avoids the systemic effects of fibrinolysis and may be a safer option in patients with known IE. Two recent case reports describe the successful treatment of proximal middle cerebral artery occlusions because of septic embolism with clot retrieval devices.10,11 Although publication bias may partly explain the high proportion of complications, this small series of cases supports IE as being a contraindication to thrombolysis in acute stroke. Four of the seven reported cases developed ICH, and one deteriorated clinically without ICH possibly because of further systemic embolism. The presence of IE needs to be carefully considered in patients presenting with acute stroke and being considered for tPA.

References
Two-faced haemophagocytic lymphohistiocytosis: comparative review of two cases of adult haemophagocytic lymphohistiocytosis

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Key words
Haemophagocytic lymphohistiocytosis, lymphoproliferative neoplasm, lymphoma, anaplastic large cell lymphoma, immunology.

Abstract
Haemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disease of children and adults. Cytokine dysfunction, uncontrolled accumulation of activated T-cells and histiocytes, and the inability to terminate the immune response lead to the clinical manifestations of extreme inflammation and end-organ damage. HLH is notoriously underreported because of its ability to mimic many other common diseases. Here, we outline two cases of HLH, one primary and the other secondary, to highlight some of the differences and to discuss therapeutic principles and emerging concepts.

Haemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disease of children and adults. The disease is broadly classified into primary and secondary HLH. Primary HLH is where there is a genetic predisposition for developing the disease. Secondary HLH is due to an underlying condition such as infection, autoimmune disease, malignancy or a metabolic condition. Epstein–Barr virus (EBV) is the most common viral infection implicated in secondary HLH, and of particular relevance to haematologists are the malignant associations with lymphomas and leukaemias, especially of the T and NK cell types.1 Whereas in the past, primary and secondary HLH were felt to be distinct disease entities and mutually exclusive, now there is the emerging view that they are a continuum. In fact, the particular genetic mutation present alters a patient’s threshold for developing HLH and the subsequent disease manifestations.2

A 20-year old man presented with high fevers, nausea, vomiting, diarrhoea and right upper quadrant pain. He was diagnosed with HLH 23 months previously at another institution after presenting with high fevers and multiple organ dysfunction. This initial presentation was triggered by primary infection with EBV. Of note, there was no consanguinity in the family. His initial investigations revealed a mild thrombocytopenia of 135 × 10⁹/L but normal haemoglobin and white blood cell count. He had a coagulopathy with an increased activated partial thromboplastin time of 42.6 s and prothrombin time of 18.8 s, and a decreased fibrinogen of 1.8 g/L. He had hyponatraemia with a sodium of 132 mmol/L, slightly abnormal liver function tests and normal triglycerides, but a markedly elevated ferritin of 8025 μg/L. Autoimmune serology was negative. Parvovirus serology showed a positive immunoglobulin M and equivocal IgG, with a positive parvovirus polymerase chain reaction (PCR). A computed tomography (CT) scan showed axillary lymphadenopathy and splenomegaly. Fine-needle aspiration biopsy of axillary and inguinal nodes showed histiocytic aggregates but no malignant cells. He underwent a bone marrow aspirate and trephine biopsy that showed changes consistent with parvovirus infection including erythropoiesis arrested in the proerythroblastic stage, as well as haemophagocytosis (Fig. 1). There was no evidence of lymphomatous involvement. His fevers worsened as did his cytopenia and coagulopathy. He was commenced on high-dose dexamethasone 10 mg/m² and given intravenous immunoglobulin to assist him with clearing the parvovirus. He responded rapidly, and the steroids were weaned and eventually stopped. Only 2 weeks after stopping the steroids, he developed recurrent
HLH and was restarted on dexamethasone, etoposide and cyclosporin, as per the HLH 2004 protocol. One week after starting the cyclosporin, he developed seizures with loss of consciousness and hypertension. A magnetic resonance imaging (MRI) showed changes favouring posterior reversible encephalopathy syndrome (PRES), and he was commenced on the anticonvulsant levetiracetam. Given the patient’s age, he went on to have other investigations. He was found to have reduced NK cell functional activity and reduced perforin (PRF1) expression, the latter of which can be decreased in active disease irrespective of the presence of a genetic defect. Testing for PRF1 mutations was negative. Signaling lymphocytic activation molecule (SLAM)-associated protein (SAP) expression was normal, excluding X-linked lymphoproliferative disease type 1. MUNC 13-4 mutation testing was still being performed at the time of writing this article.

At present, the patient remains well on maintenance therapy with dexamethasone, etoposide and cyclosporin. He has been referred for allogeneic transplant using his 23-year-old histocompatible sister as the donor. She has normal NK cell function and PRF1 expression, and has had EBV and cytomegalovirus infections without the development of complicating HLH.

A 64-year-old woman presented to a district hospital with a 7-week history of anorexia, weight loss, sweats, lethargy and dehydration. Her initial investigations showed thrombocytopenia with platelets of $99 \times 10^9$/$L$, hyponatraemia with a sodium of 123 mmol/L, and an elevated serum ferritin of 2200 μg/L. A CT scan revealed abdominal lymphadenopathy. A CT of her brain was normal. She was rehydrated with saline and discharged. She represented to the district hospital 10 days later with hypotension, pancytopenia and worsening hyponatraemia. She was transferred to our institution after 24 h. Investigations showed a worsening thrombocytopenia with a platelet count of $46 \times 10^9$/L, worsening hyponatraemia with a sodium of 116 mmol/L, coagulopathy, abnormal liver function tests raised ferritin of 17 158 μg/L and fasting triglycerides of 4.2 mmol/L. Virology returned a positive EBV PCR. She underwent a bone marrow biopsy (Fig. 2) that was hypercellular with prominent haemophagocytosis. The trephine showed dense histiocytic aggregates and scattered large pleomorphic cells staining positive for CD30. Fluorescence in situ hybridisation was then performed on the marrow paraffin slides, and when correlated with the CD30-positive cells found a small population of cells with non-rearranged anaplastic lymphoma kinase (ALK). The diagnosis was confirmed as haemophagocytic syndrome secondary to anaplastic large cell lymphoma of the ALK-negative subtype. She was started on chemotherapy as per the HLH-94 protocol consisting of daily dexamethasone and etoposide twice weekly. A single
A dose of rituximab was given following the positive EBV PCR result.

Her admission was complicated by febrile neutropenia. She also developed focal seizures at the onset of sepsis, and an MRI showed the classic changes of PRES, so she was started on the anticonvulsant levetiracetam. She has now started chemotherapy (cyclophosphamide, adriamycin, vincristine, etoposide and prednisone) for the T-cell lymphoma.

While these cases both represent the same disease entity, they highlight some differences. The first case was seen in a young patient who had primary HLH, who was found to have reduced NK cell function and reduced PRF1 expression. The second case was seen in an older patient and was secondary HLH because of an underlying T-cell lymphoma. As a consequence of the underlying aetiology, the first case received induction chemotherapy followed by referral for allogeneic stem cell transplant, whereas the second case received dexamethasone, and therapy targeted specifically at the underlying T-cell lymphoma, without the need for allogeneic stem cell transplant.

Figure 2  (a) Bone marrow aspirate (×20; May Grunwald-Giemsa (MGG)) showing haemophagocytosis of neutrophils and an erythrocyte. (b,c) Bone marrow aspirate (×40; MGG) showing further examples of haemophagocytosis seen throughout this patient’s marrow. (d) Trephine (×10), haematoxylin and eosin (HE): showing a paratrabeicular histiocytic aggregate admixed with anaplastic large lymphoma cells. (e,f) Trephine (×40, HE) showing a histiocytic aggregate distorting the normal marrow architecture and within the aggregate a large, multinucleated lymphoma cell. (g,h) Trephine (×20, ×40; CD30 immunohistochemical stain) showing the large, anaplastic lymphoma cells with membranous CD30 positivity.
A recent article in Blood by Jordan et al. provided a guided schema on the genetic work-up suggested in cases of suspected primary HLH. They suggest a rapid immunological work-up in days (consisting of the following tests if available: PRF1/granzyme B protein expression, CD107a mobilisation, SAP and protein expression in males only), followed by a more comprehensive genetic work-up in the subsequent weeks (as listed in Diagnostic Criterion A of Table 1). An abnormal immunological test suggests an underlying genetic abnormality. However, a normal immunological test does not preclude genetic testing. The difficulty in Australia is that not all genetic tests are offered in this country, assays are still being developed and methods are being perfected; there is a lack of centralisation and standardisation of testing, and there is significant delay in obtaining results.

Whereas in the past, primary and secondary HLH were felt to be distinct disease entities and mutually exclusive, now there is the emerging view that they are a continuum. In fact, the particular genetic mutation present alters a patient’s threshold for developing HLH and the subsequent disease manifestations. With improvements in diagnostics, new markers are finding relevance in the diagnosis of HLH. Soluble interleukin 2 receptor (sIL2r or sDC25) is one such marker, which reflects the degree of T-cell activation. It is useful in diagnosis and follow-up because very high levels are almost never seen outside of HLH. It therefore correlates with current disease activity more consistently than ferritin or other disease indices and is therefore part of the revised diagnostic criteria for HLH. Another new marker is soluble CD163 (sCD163) that is a receptor for haemoglobin-haptoglobin complexes and is a marker for activation of alternative-pathway scavenger macrophages. According to Weitzman, plasma levels of sCD163 in HLH are considerably higher than those found in infections, autoimmune diseases and cancer.

HLH is a disease being recognised with increasing frequency in adults, and it is important to appreciate the poor prognosis of the condition, with primary HLH being universally fatal if untreated with a median survival of <2 months. It is important to recognise the disease early and institute timely and aggressive management to reduce mortality and morbidity of the disease, even if genetic testing remains incomplete.

Table 1 Diagnostic criteria for HLH (based on HLH 2004 protocol)

| A. Molecular diagnosis consistent with HLH with no evidence of underlying malignancy. | B. Five of the eight criteria listed below are present: |
| Pathological mutations found in at least one of the following: |  |
| PRF1 | Fever ≥38.5°C |
| UNC13D | Splenomegaly |
| Rab27a | Cytopenias (affecting at least two of three lineages in peripheral blood) |
| STX11 | Neutrophils <1 × 10^9/L |
| SH2D1A | Platelets <100 × 10^9/L |
| BIRC4 | Hypertriglyceridaemia (fasting >265 mg/dL) |
| | and/or hypofibrinogenaemia <1.5 g/L |
| | Haemophagocytosis in bone marrow, lymph nodes, liver or spleen |
| | Low or absent NK cell activity |
| | Ferritin >500 ng/mL (ferritin >10 000 ng/mL is highly suspicious of HLH) |
| | Elevated sCD25 (alpha chain of sIL2 receptor) above age-adjusted, lab-specific normal levels, that is, >2SD from mean. |

Adapted from Jordan et al. BIRC4, baculoviral IAP repeat-containing protein 4; PRF1, perforin 1; SH2D1A, Src homology 2 D1A gene; STX11, Shiga-toxin gene 1.

While HLH is reported to be a rare disease, it is the one that is increasingly recognised in adults. Given the ability of HLH to mimic other common diseases, a high index of suspicion is needed among clinicians so that the diagnosis is not missed. It should be particularly excluded in the context of a T-cell or NK cell leukaemia or lymphoma, especially if there is acute deterioration of the patient or the development of multiple organ dysfunction. Table 1 illustrates the diagnostic criteria for HLH. The diagnosis may be established if A or B is satisfied.

An understanding of the pathogenesis of HLH is important. The genetic mutations implicated are involved in the cytolytic secretory pathway. This pathway is important in delivering preformed granules such as PRF1 and granzymes to the synaptic junctions between NK cells or cytotoxic (CD8) T-cells and their target cells. Genetic defects have been detected at various steps in this normal cellular mechanism and result in defective termination of the immune response, persistent activation of macrophages and cytotoxic T-cells, and failure to remove antigen, with resulting ongoing stimulation of immune effector cells.

References


TELEHEALTH SERIES

Practical aspects of telehealth: establishing telehealth in an institution

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Key words
telehealth, video consultation, telemedicine, Townsville Teleoncology Network, teleoncology.

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Abstract
The fifth in a series of papers on practical aspects of telehealth, this paper discusses telehealth models that can facilitate the provision of specialist services to rural and remote patients closer to home. Some of the barriers to successful implementation of these models relates to workforce, funding and infrastructure at rural sites, as well as the traditional mindset of healthcare professionals. Therefore, the rural sector needs to be adequately resourced for telehealth models to be substantive and successful. This paper describes the development of a large teleoncology network over a vast geographical area in North Queensland. Adequate resourcing for the rural sites and undertaking quality improvement activities has continually enhanced the model over a 5- to 6-year period. The benefits of this model of care are twofold: (i) patients received their care closer to home and (ii) the workforce, service capabilities and infrastructure for the hospital in Mt Isa (a rural town 900 km away from its tertiary centre) has improved.

Introduction
The provision of specialist medical services in many rural and remote towns is hampered by workforce shortages, narrow scope of practice and limited service capabilities.1,2

Telehealth models in cancer care (hereafter referred to as teleoncology) can facilitate the provision of specialist cancer services closer to home. Teleoncology has been adopted by many centres to provide specialised care to rural and remote communities in many countries.3,4

A successful telehealth model relies on motivated providers, an adequate workforce and sufficiently resourced remote facilities. Consequently, to build a telehealth network, it is important to ensure the growth of capacity at remote sites in parallel with the providing sites.7 In the literature, many factors have been identified as barriers to the uptake of telehealth.8 These include: lack of funding; extra time commitment for rural doctors and the resultant impact on workload; insufficient infrastructure; equipment, technology and skills; and a preference for a more traditional approach.

The department of medical oncology of the Townsville Cancer Centre (TCC), the tertiary cancer centre for Northern Queensland (Australia), services a large geographical area of more than 300 000 km². The largest rural town in its catchment is Mt Isa, 900 km west of Townsville with a population of 20 000. In 2007, TCC embarked on establishing a network to provide cancer care to rural towns through telehealth. Because most rural Queensland health hospitals were already fitted with videoconferencing technology at the time, the coordination and mobilisation of human resources were the next steps in establishing the Townsville Teleoncology Network (TTN).

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Objective

In this paper, we attempt to show that service capability and scope of practice in rural hospitals can be enhanced by providing specialist services in rural towns through telehealth services modelled on the Townsville-Mt Isa experience.

Case study: development of the TTN model

To illustrate the gradual and reflective development of the Townsville-Mt Isa model within the TTN, the sequence of events leading to the current operational structure has been summarised as:

1. Service capability of Mt Isa Hospital prior to the establishment of the TTN
2. Selection of levels of services to be provided
3. Establishment of the TTN model of care
4. Expansion and refinement of the model.

Service capability of Mt Isa Hospital pre-teleoncology model of care

Prior to the introduction of teleoncology, cancer patients were managed by the emergency department at Mt Isa Hospital on a goodwill basis. There were two nurses who had some competency in administering chemotherapy.

Mt Isa Hospital had an internal medicine physician who could be called upon for help, a radiology facility with computer tomography and biopsy capability, an intensive care unit for less complex cases and pathology had a turnaround time of less than 60 min for blood tests.

In terms of cancer care services, there were three chemotherapy chairs occupied for 2 days a week. All patients had to travel to TCC for their first consultation and for reviews. All the first doses of chemotherapy were given at the TCC. Moderately toxic regimens were given subsequently at Mt Isa Hospital. Highly toxic regimens were given at TCC.

Selection of level of activities

The selection of sites for chemotherapy was based on the service capability of each site as per the Queensland Health Service Capability Framework (SCF). In the SCF, hospitals are assigned levels from 3 to 6. A Level 3 service provides low-risk ambulatory care, whereas a Level 6 service provides comprehensive cancer care including bone marrow transplant and high-risk chemotherapy protocols. Mt Isa Hospital was selected for providing more comprehensive medical oncology services given the already existing Level 3 chemotherapy facility.

Establishment of TTN

2007–2009

The network between Townsville and the rural sites was established in May 2007 by informal arrangements between the TCC department of medical oncology and health professionals at rural sites. Videoconferencing equipment was installed in meeting rooms at rural sites. At the tertiary centre, equipment was installed in meeting rooms and offices. Patients were booked via medical oncology clinics in Townsville, and consultations were undertaken using the videoconferencing equipment. Prior to the commencement of each consultation, patients were asked to sign an informed consent form for participation in this model of care. Patients declining consent were offered the option of travelling to Townsville, as was the usual practice prior to 2007.

Mt Isa Hospital staffing and professional development

Extra training was provided at the TCC for two nurses to gain competency in administering complex regimens at Mt Isa Hospital. Senior Medical Officers from the Emergency Department were formally rostered to facilitate the videoconference sessions. The medical oncology handbook used for junior doctors at the TCC was shared with the doctors in Mt Isa for reference purposes. Each case discussion via video link also served as an occasion for continuing medical education for rural doctors.

Service capabilities

Between 2007 and 2009, patients travelled to Townsville for the first consultation with medical oncologists. Patients from Mt Isa were subsequently managed through videoconferencing. For chemotherapy treatment, patients travelled to Townsville for their first treatment and were able to receive subsequent doses in Mt Isa, except for toxic regimens like bleomycin, etoposide and platinum; ifosfamide; and methotrexate infusions.

Expansion and refinement of TTN model

2009–2012

Given the increased activity at Mt Isa Hospital, TCC was successful in securing additional funds from Queensland Health to build capacity for the TTN in Mt Isa. Once all involved parties became comfortable with this model of care and the increased work force, the following decisions were made: (i) all new patients could be seen first via videoconferencing to make sure their future care was...
coordinated if, and when, patients travelled to Townsville; (ii) patients from Mt Isa did not need to travel to Townsville unless requested by the patients or the treating teams; (iii) all solid tumour chemotherapy regimens could be administered in Mt Isa; and (iv) all admitted inpatients were to be seen by medical oncologists in ward rounds via videoconferencing.

Clinic model

Details of the clinic model have been published previously. Patients and their families were joined by chemotherapy competent nurses, senior and junior medical officers, and allied health practitioners during consultations. At other sites, either a doctor or a nurse sat in with patients, if required. Details of the consultations were documented in medical charts and summary letters sent to general practitioners and referring doctors.

Quality assurance

As part of refining the model, several quality assurance activities were undertaken:

1 Patient satisfaction surveys (these revealed satisfaction of more than 96% by patients)
2 Indigenous and non-indigenous health professional perspectives (there was overwhelming support from both for this model)
3 Audits of safety of remote supervision of chemotherapy (study ongoing)
4 Mortality and morbidity meetings.

Outcomes on workforce and service capabilities

As the result of the teleoncology model of care, the level of services provided at Mt Isa Hospital has escalated, as in Table 1, to SCF Level 4. The numbers of oncology specific staff have also increased to a part time Senior Medical Officer, a shared basic physician trainee rotating from Cairns, a Resident Medical Officer, a Cancer Care Coordinator, two chemotherapy nurses, Aboriginal liaison officers and others, as required.

Increased staff numbers, outpatient and chemotherapy occasions of service, together with comprehensiveness of the service provided locally, led to success in securing regional cancer centre funds from the Commonwealth Government to build a five-chair state of the art chemotherapy facility in Mt Isa.

Discussion

One of the main reasons for the success of the teleoncology model of care was the expansion and capacity building of remote sites to accommodate services from TCC. As most of the barriers are related to the resourcing levels at the receiving rural sites, it is logical to identify and rectify them at the outset to enable buy-in from rural sites.

The selection of sites for chemotherapy was based on the service capability of each site as per Queensland Health SCF. SCF can be followed in two ways. One approach is to avoid sites that do not meet the criteria for further development and the other, more proactive approach, might be to select the sites for new service developments and work on resourcing them adequately, to the point that they meet the SCF, as has been done for Mt Isa.

Over the years, as depicted in Figure 1, Mt Isa has become a complete medical oncology unit with specialist medical oncologists available on demand through videoconferencing supported by rural health professionals. Now, it has the capacity to provide all solid tumour

Table 1

<table>
<thead>
<tr>
<th>Town</th>
<th>Specialist cancer clinic via videoconference</th>
<th>Patient types</th>
<th>Chemotherapy</th>
<th>Comment on travel to and from Townsville</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mt Isa</td>
<td>3–4 times per week and on demand</td>
<td>All new and reviews, urgent ward consults</td>
<td>All solid tumour regimens</td>
<td>No need for travel by patients and specialists</td>
</tr>
</tbody>
</table>

Figure 1 A model of a rural specialist unit with specialist support via a telehealth model of care.
Disease progress in patients with Morbus Fabry after switching from agalsidase-beta to agalsidase-alpha

In Fabry disease (FD), two recombinant substances, agalsidase-alpha (Replagal; Shire Corp., Lexington, MA, USA; produced in human fibroblasts) and agalsidase-beta (Fabrazyme; Genzyme Corp., Cambridge, MA, USA; produced in a Chinese hamster ovarian cell line) allow enzyme-replacement therapy (ERT) that leads at least to short-term stabilisation of renal and cardiac manifestation, the main drivers of mortality.1-10 In June 2009, Genzyme Corp. halted production after a virus (vesivirus-2117) was discovered in the production equipment at its plant in Allston, MA, USA, which finally led to a relevant global shortage of agalsidase-beta.11 As a consequence, many patients that were treated with agalsidase-beta received a reduced dose or had to be switched to agalsidase-alpha.

We assessed the effects of the shortage in our FD cohort database in Zurich/Switzerland in five male patients that had to be switched compared with five matched, male patients under continuous treatment with agalsidase-beta (‘control group’). Both groups were matched regarding age, disease severity and additional drug therapy (e.g. angiotensin-converting enzyme inhibitors). The intention to start ERT with either one of the two substances, initially, based on the personal choice of the physician and not on specific clinical conditions (e.g. disease severity).

Our data confirmed the results of two former surveys,12,13 and according to their end-point definitions,
no adverse events occurred within the ‘switched’ group during 2-year follow up (death, neurological events, progression of renal disease with a decrease of estimated glomerular filtration rate to <15 mL/min/1.73 m² using the Modification of Diet in Renal Disease (MDRD) formula, kidney transplantation, dialysis, increase in plasma creatinine of more than 33% on two consecutive years and cardiac events). Moreover, according to additional criteria (further nephrologic and echocardiographic measures) relevant disease progress could be suggested in 2 patients of our control group (proteinuria, increase of serum creatinine under constant ACE inhibitor therapy; Fig. 1).

Although the number of patients was small, our study provided extended observational time and increased accuracy of the assessment. Nevertheless, studies with larger cohorts and longer follow-up will still be needed to confirm these findings, and it still remains uncertain whether changes in renal or cardiac measures are just a reflection of a ‘natural’ disease progression.

However, the results of now three small observational studies are not in line with a highly regarded report of the European Medicines Agency (EMA), which proclaimed an obvious increase in adverse events since the start of the shortage. It certainly has to be made on an individual basis. It is, however, remarkable that irrespective of the context of drug shortage, there is only one study that examined differences concerning the effectiveness of agalsidase-alpha and agalsidase-beta at an equal dose, and the superiority of either one of the substances has not been proven so far.

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Successful management of life-threatening disseminated intravascular coagulopathy due to metastatic melanoma

The management of acute disseminated intravascular coagulopathy (DIC) due to solid tumour malignancies can be challenging, as treating the underlying cause with cytotoxic chemotherapy may have limited effectiveness and significant toxicity. The advent of targeted therapies for malignancies is changing the treatment landscape. We report the successful management of a patient with a life-threatening coagulopathy due to BRAF-mutated melanoma.

A 62-year-old woman presented to the emergency department with haematuria. She had been diagnosed with metastatic melanoma 2 months earlier after presenting with a generalised seizure and a rapidly growing mass on her left arm. Imaging had revealed a 5-cm right parieto-occipital brain lesion and a mass in the left arm, but no evidence of other disseminated disease. Biopsy of the cutaneous mass and surgical excision of the brain lesion revealed that both were melanoma. Three weeks prior to the current presentation with haematuria, she completed radiation therapy to the fungating arm lesion and to the whole brain in the context of a phase 3 randomised controlled trial.1

Laboratory studies demonstrated anaemia (haemoglobin 53 g/L) and thrombocytopenia (90 × 10⁹/L), together with a raised prothrombin time (18.8 s), markedly elevated D-dimers (>10 mg/L) and very low fibrinogen level (0.8 g/L), consistent with overt DIC. Lactate dehydrogenase was elevated (929 U/L), and renal and hepatic function were normal. Blood film examination revealed reduced platelets and occasional fragments, but no leukoerythroblastic reaction. A complete septic screen was negative, and the clinical picture was that of DIC secondary to the patient’s underlying malignancy.

She required daily transfusions of packed red blood cells, cryoprecipitate, fresh frozen plasma and pooled platelets to manage her coagulopathy, but despite aggressive blood product replacement, her condition progressively declined. Molecular studies on her tumour tissue revealed a BRAF V600E mutation raising the possibility of treatment with a targeted BRAF inhibitor. The potential risks of giving our patient with a poor performance status...
Schlaeppi and colleagues reported a case of DIC because of melanoma that resolved with combination chemotherapy including dacarbazine, vinblastine and cisplatin. In another report, a patient with haemorrhagic shock due to melanoma-related DIC died despite treatment with dacarbazine chemotherapy. A series of cases of DIC following injection of bacillus Calmette-Guerin (BCG) into cutaneous melanoma nodules has been reported. The coagulopathy in these cases was felt due to an intense immune response to BCG rather than being tumour antigen provoked, and all four patients survived with intensive supportive care and anti-mycobacterial antibiotic therapy.

Research in recent years has revealed distinct mutations in melanoma, and around half the cases of metastatic melanoma harbour a B\textsuperscript{RAF} V600 mutation. Vemurafenib was shown to improve survival with a response rate of 48% (compared with 5% in the dacarbazine chemotherapy control arm) in B\textsuperscript{RAF} V600E-mutated melanoma in the BRAF Inhibitor in Melanoma-3 (BRIM-3) trial. It is likely that our patient would have succumbed to her disease when she presented with acute DIC if treatment with a B\textsuperscript{RAF} inhibitor was not available. The advent of effective, targeted treatments for B\textsuperscript{RAF}-mutated melanoma makes treatment in this type of situation possible, and rapid responses can be achieved.

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General correspondence

Adult medulloblastoma: feasibility and effectiveness of utilising high-dose chemotherapy with autologous stem cell rescue in newly diagnosed patients

We read with great interest the recent article by Wong et al.,1 reporting their local experience of treatment of adult medulloblastoma including adjuvant chemotherapy based on paediatric protocols.

We fully agree with their conclusions in terms of the potential to achieve long-term disease-free survival with this approach and would like to report our own experience in treating adult patients with medulloblastoma and atypical teratoid/rhabdoid tumours with adjuvant chemotherapy based on the previously published St Jude paediatric protocol.2,3

Since January 2003, all adult patients with newly diagnosed medulloblastoma and atypical teratoid/rhabdoid tumours at our institution have been treated on a standardised pathway including surgical resection followed by craniospinal irradiation (CSI; 36 Gy with 18.8 Gy boost to the tumour bed) and subsequent sequential cycles of high-dose chemotherapy with autologous stem cell support.

Peripheral blood stem cells were harvested post-G-CSF mobilisation pre-CSI; adjuvant chemotherapy was commenced 6 weeks post-CSI and consisted of 4 monthly cycles of high-dose cisplatin, cyclophosphamide and vincristine, as previously published.2,3 Patients were identified from an institutional database and outcomes retrospectively determined by review of individual patient records.

As of January 2012, we have treated a total of seven adult medulloblastoma or atypical teratoid/rhabdoid tumour patients on the St Jude protocol. Median patient age at diagnosis was 24.5 years (range 19–37 years) with 71% male (Table 1). As per modified Chang criteria, six (86%) had standard-risk disease and one (14%) high-risk features at diagnosis. A further two patients (28%) had poor-risk cytogenetic features identified (gain of 17q and loss of 17p).4–6 At a median follow-up post-diagnosis of 65 months (range 11–109 months), six patients (86%) remain alive and disease-free with only one patient experiencing relapse/death (Fig. 1). This patient relapsed at 9 months post-diagnosis and subsequently died of progressive disease 2 months later.

Overall treatment was well tolerated, with no treatment-related deaths observed. Overall mean and median number of chemotherapy cycles delivered per patient was 3.85 and 4 respectively (range 3–4). The main

Table 1 Patient demographics, disease features and outcome

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Histology</th>
<th>Chang risk stratification</th>
<th>Cytogenetics</th>
<th>Molecular subgroup</th>
<th>Residual tumour post-resection</th>
<th>FU (months)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>17</td>
<td>Atypical teratoid/rhabdoid tumour</td>
<td>Standard</td>
<td>Normal</td>
<td>NA</td>
<td>None</td>
<td>85</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>37</td>
<td>Nodular desmoplastic tumour</td>
<td>Standard</td>
<td>Trisomy 17q21</td>
<td>SHH</td>
<td>None</td>
<td>28</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>37</td>
<td>Nodular desmoplastic tumour</td>
<td>Standard</td>
<td>NA</td>
<td>SHH</td>
<td>None</td>
<td>108</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>24</td>
<td>Nodular desmoplastic tumour</td>
<td>High</td>
<td>NA</td>
<td>SHH</td>
<td>2.4 cm²</td>
<td>79</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>18</td>
<td>Classic medulloblastoma</td>
<td>Standard</td>
<td>NA</td>
<td>SHH</td>
<td>1.4 cm²</td>
<td>11</td>
<td>Dead</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>27</td>
<td>Nodular desmoplastic tumour</td>
<td>Standard</td>
<td>P53 deletion</td>
<td>SHH</td>
<td>None</td>
<td>65</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>21</td>
<td>Nodular desmoplastic tumour (pauci-nodular variant)</td>
<td>Standard</td>
<td>NA</td>
<td>SHH</td>
<td>None</td>
<td>44</td>
<td>Alive</td>
</tr>
</tbody>
</table>

FU, follow-up; NA, not available; SHH, Sonic Hedgehog pathway.

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complications of therapy included febrile neutropenia (44% of cycles), grade 3 ototoxicity (33% of cycles), grade 2 renal toxicity (15% of cycles), grade 3 hepatic toxicity (11% of cycles) and grade 3 central nervous system toxicity (4% of cycles). All living patients were contacted by phone in late 2012 by the treating institution, and all reported ‘good’/’normal’ functional status.

As per the experience of Wong et al.,1 patients with standard-risk disease appeared to achieve excellent outcomes with medial survival not yet reached. However, unlike the experience of Wong et al.,1 all three patients with poor-risk disease features in our series (as per modified Chang criteria or cytogenetic findings) remain alive and disease-free at ≥28 months (range 28–79 months) post-diagnosis.

Given the rarity of medulloblastoma in adult populations, it is unlikely that randomised trials will ever be feasible in this patient group. However, comparison of standardised treatment approaches across institutions may still allow for interpretation of different treatment regimens in adult patients. Our experience suggests that the St Jude protocol consisting of CSI followed by sequential high-dose chemotherapy with autologous stem cell support is well tolerated and associated with encouraging outcomes in adult patients with medulloblastoma, including in those with poor-risk disease features.

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References

Author reply

We thank Collins et al.1 for their interest in our paper.3 Data from Collins et al.1 regarding the use of high-dose chemotherapy/autologous stem cell rescue (HDCT/ASCR) in patients with de novo adult medulloblastoma are thought provoking.

Previous series had reported 5-year survival of 70–80% in low-risk adults, regardless of whether adjuvant chemotherapy was administered.1,4 The outcomes described by Collins et al.1 are encouraging but appear comparable with published literature for this group of patients. Our own series2 did not find that the use of a more intensive treatment using a triplet chemotherapy regimen improved survival in low-risk patients compared with the doublet regimen although there are clearly caveats to this conclusion. Although the toxicities of HDCT/ASCR were manageable by the authors who are experienced with this approach, the rates of treatment-related mortality are concerning, with rates ranging from 12% to 26%.3–8

The use of HDCT/ASCR in high-risk or relapsed adult patients may be more appealing to clinicians given the much poorer prognosis of these patients. The outcomes of the three patients in the study by Collins et al.1 are certainly suggestive. Efficacy in the recurrent setting provides some support. A recent series of six adult patients with recurrent disease showed median survival of 21.5 months, with one patient developing multi-organ failure.
requiring life-sustaining therapy.\textsuperscript{5} Dunkel \textit{et al.}\textsuperscript{6} had also reported on 25 patients with previously irradiated disease aged 7.6–44.7 years (median 13.8 years) who achieved median survival of 26.8 months.

We were also interested in the use by Collins \textit{et al.}\textsuperscript{1} of molecular phenotyping as an adjunct to conventional risk stratification in their patients. It has been increasingly appreciated that adult medulloblastoma comprised distinct molecular subtypes that are age-specific and prognostically significant that are age-specific and prognostically significant.\textsuperscript{10} Korshunov \textit{et al.}\textsuperscript{11} had previously proposed molecular stratification of adult medulloblastoma using an evaluation of 17q gain and 10q loss.

Overall, we found the data by Collins \textit{et al.}\textsuperscript{1} to be very interesting with thought-provoking results. Ultimately, the treatment approach should be individualised for each patient. However, given the toxicities of HDCT/ASCR, we would advocate that this be attempted only in experienced treatment centres. We would support the development of a nationwide collaborative approach towards the treatment of adult medulloblastoma, for example, utilising the Cooperative Trials Groups for NeuroOncology to design a trial and acquire useful prospective data on this rare disease.

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\textbf{References}


Corrigendum

The publisher would like to draw readers’ attention to an error in affiliation for the co-author Emily Allen in the article below published in the October 2013 issue of the Journal.


On page 1103, the affiliation for Emily Allen is stated as ‘Royal Prince Alfred Hospital, Sydney’ but should read ‘Haematology, Prince of Wales Hospital, Sydney’.

The corresponding author apologises for the error in the article and for any confusion caused.
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