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Advances in Hodgkin lymphoma

Lyme disease

Non-melanoma tumours and pembrolizumab

Alcoholic liver disease

Chronic fatigue

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OBITUARY

Henry Joseph Macauley Barnett, 1922–2016

Henry Joseph Macauley (H. J. M.) Barnett or 'Barney' as he was known died peacefully in Toronto on 20 October 2016 at the age of 94 with his family around him.

Barney had a passion for life and embraced everything he did with enthusiasm. It is said that most researchers have the energy to undertake one randomised controlled trial, Barney together with his colleague Vladimir Hachinski and their colleagues from McMaster University, Dave Sackett, Brian Haynes and Wayne Taylor undertook not one but three pivotal studies to evaluate the therapy of stroke.

The first was the Canadian aspirin study. When planning the study, they were trying to decide the dose of aspirin to use. The meeting was in a hotel room at Montréal airport where it was decided to use the same dose of aspirin that rheumatologists were using at the time to treat rheumatoid arthritis, 1200 mg. Although we now know that a much smaller dose is adequate, this trial proved for the first time that aspirin helped to reduce the risk of subsequent stroke.

On completion of the second study, the extracranial to intracranial (EC-IC) bypass study showing that the procedure did not prevent stroke, they were told that 'the study had to be wrong!' I worked with Barney on the EC-IC bypass study and towards the end there were 2 patients missing, not bad out of 1377 patients. Most researchers would accept this, however, this was not good enough for Barney who then employed a detective to find (successfully) the last two patients in the United States. This trial had a 100% follow-up which is extraordinary for any study, in particular a study that spanned many years.

The third trial was the North American Symptomatic Carotid Endarterectomy Trial. Prior to this study, physicians and surgeons used to argue vehemently as to who should and who should not have the procedure. It took less than 700 patients to stop the arguments that had been going on for many years. The study showed that patients with a symptomatic stenosis of more than 70% clearly benefited while patients with a stenosis of 50–70% had moderate benefit with a carotid endarterectomy. When they completed this trial, they were told 'we already knew the answer!'

I first met Barney in 1983 when I went from Newcastle upon Tyne in the United Kingdom (his birthplace) to work with him in London, Ontario. Charlie Drake, the doyen of giant basilar aneurysm surgery, was the head of neurosurgery and Barney was the head of neurology.

Barney was definitely a 'lark'; he had usually finished a day's work before most people were even out of bed. His secretaries used to try and guess where he was when

he was dictating. This was often in the car as his wife Kay who he loved dearly drove him to their rural property at King just north of Toronto, another of his great loves. Sadly, Kay predeceased him by many years.

Barney's other great love was nature and in particular birds. He was a formidable 'twitcher' or ornithologist who could recognise a bird simply from its call. He was very much involved with the Nature Conservancy of Canada. The 70 acres of his property at King is part of 700 acres of land preserved forever.

Barney was an inspiration to everyone who worked with him. One of his favourite quotations was that the plural of anecdote is not science. He was a giant in his time. His advice to young aspiring neurologists was to see as many patients as they could in the first 20 years of their career. Those of us who knew him personally will miss the wonderfully cheeky smile that punctuated his look of determination.

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EDITORIAL

Enough is enough … a call to action to improve ethical and governance review processes in Australia

All research should be conducted in an ethically responsible manner, ensuring that institutions and researchers uphold the rights of study participants, understand their obligation to report research misconduct, are appropriately equipped and trained to undertake the project and have appropriate governance and management structures in place to safeguard study participants and themselves. These obligations are set out in documents developed by peak research bodies and government agencies and are assessed by properly constituted, institutional ethics committees and research management groups within the institution in which the research is to be conducted.[1,2]

Ethics committees are required to review research which carries more than a 'low' level of risk (defined as research in which the only foreseeable risk is one of minimal discomfort to study participants). However, although the efficiency of this process has improved substantially in recent years, enabling a single ethics committee which is appropriately credentialed to assess and approve research in multiple sites around Australia,[3] there is still room for improvement. At face value, this process of so-called mutual acceptance sounds like a huge leap forward and one which will fast-track research and translation of innovation into practice. However …

As documented by White *et al*. in the September 2016 issue of the *Internal Medicine Journal*, even with centralised ethical review in place in five of the six jurisdictions where their research was undertaken, the process was often slow, duplicative, inconsistently implemented and generally poorly coordinated.[4] The ethical review process took on average 6.5 weeks to approve, ranging from 2 to 18 weeks. In this case, the research was considered 'high-risk' as it required the release of identifiable patient information, yet it did not involve any intervention per se. It is not clear whether these multiple reviews improved the quality of the research planned or if they reduced the risk to participants, researchers or institutions.

Compounding the problem, site-specific research governance approvals were required in 60% of institutions in jurisdictions using the centralised ethics review system. Site-specific governance is intended to ensure that 'institutional considerations about undertaking research in the context of the institution's policies, strategic priorities, expertise, resources, contractual arrangements, financial issues and approach to risk management' are considered.[5] This process usually commences after ethics approval has been issued. White *et al*. reported that this process took on average nearly 10 weeks, with a range from 1 to 45 weeks and a median time of 6 weeks. The waste of time and money, and the gross inefficiency demands we admit that the current system is in urgent need of resuscitation.

The study by White *et al*. was implemented in 67 hospitals. Ethical and governance approvals delayed their project by more than a year. Perhaps herein lies the true cost of such inefficiency: delays in the completion of important research designed in this case to improve the care of patients with life-threatening diseases. Unfortunately, this case is not an isolated example. Brown *et al*. recently reported that the average cost to *each* research institute of obtaining ethics approval from 52 separate hospitals was $3600 (in total amounting to $187 200), accounted for principally in wages of research assistants (96%).[6] Brown *et al*. reported a median time from application to approval of 12 weeks, double that reported by White *et al*. in the *Internal Medicine Journal*. This might be accounted for by the fact that in their timelines White *et al*. did not include any delays that ensued from researchers responding to issues raised by the ethics and governance committees.

In Europe, the 2001/20/EC Directive set out requirements for the conduct of clinical trials involving medicinal products for human use, stating that the time from researchers making a request to a definitive decision may not exceed 60 days, with an extension of a maximum of 30 days permitted for exceptional circumstances.[7] If clinical trials can have a benchmark of 60 days from initiation to determination, why is the time taken for low-risk non-interventional observational studies so protracted? An overhaul is required of the process and here we present some suggestions on what needs to change. We must all say 'enough is enough' and strive to resolve this situation.

By way of starting the conversation about a solution, implicit to which is the understanding that the status

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quo is unacceptable to patients, clinicians, governments, institutions or the community, we propose a four-point plan for addressing this issue:

1 Clearer distinction between the role of the ethics committee and the research governance group is required to reduce duplication of effort. A nationally consistent checklist distinguishing tasks between the two would provide confidence to both groups on their boundaries. The issue of external researchers entering premises to undertake data collection is an example of how this confusion is manifested. We propose that external researchers be credentialed by the centralised ethics committee using a standardised set of criteria and providing certificates to institutions to give confidence that this has been assessed.

2 Research coordination offices (RCOs) would be established to serve a number of hospitals that fall naturally within geographic, management or academic clusters. An inventory of RCOs serving each Australian hospital would be available to researchers. The RCOs would work with the researchers to identify the appropriate personnel within hospitals to authorise the study. The RCO would establish processes with commonly required authorisers such as Health Information Managers and Directors of Surgery/Medicine to facilitate this process.

3 There would be greater guidance on what constitutes 'low-risk research' to reduce the heterogeneity, which currently exists among governance and ethics committees. The Health Research Authority of the National Health Service in UK has produced a document titled 'No Material Ethical Issues Tool', which provides examples of the types of research that constitutes low-risk research.[8] Such a tool could be implemented or built upon to assist ethics committees, RCOs and researchers to harmonise the level of research risk with the type of research study being proposed.

4 Ethics and governance processes would be tracked and performance in terms of time from initiation to approval would be benchmarked across RCOs. Researchers and RCOs would be able to see how their application is progressing in a transparent process. This could be built into the National Ethics Application Form. Our experience is that there is often confusion in where the application is being held up. Such a process would have to consider where delay is occurring and not penalise RCOs who are waiting on responses from researchers. The lack of transparency and accountability at present significantly hampers efforts to improve the review process.

White *et al*. have described what are all too common, failing business processes and their impact on research in Australia. If we are to realise our aspiration of becoming an 'Innovation Nation' we must stop stifling the process for doing research and start investing in solutions.[9] Whether these four suggestions address all the issues faced by researchers begs the question that we cannot continue to accept the status quo.

Research embedded in routine healthcare is the fastest and most efficient way to improve the quality of care we provide. With increasing investment in the globalisation of clinical research, we are increasingly competing against other countries for recruitment of patients to clinical trials and cohort studies.[10] Let us use our precious resources wisely and find ways to embrace the research agenda: the community both expects and deserves nothing less.

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REVIEW

Recent treatment advances in Hodgkin lymphoma: a concise review

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Key words
Hodgkin lymphoma, PD-1, nivolumab, pembrolizumab, PET scan, brentuximab vedotin.

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Abstract

The majority of patients with Hodgkin lymphoma enjoy durable remissions following front-line treatment. This typically involves combination chemotherapy with or without radiotherapy. A significant minority of patients experience relapsed/refractory disease, of whom only approximately half can be 'salvaged' with conventional second-line treatments. Until recently, for those patients either failing or who are not fit for salvage, there have been few curative alternatives. Furthermore, there is a significant risk of delayed treatment complications to conventional therapies, including secondary malignancies and cardiac disease. However, novel targeted therapies are producing excellent results in clinical trials. They provide additional treatment options for those with relapsing/refractory disease; they may have potential in front-line therapy. The anti-CD30 antibody brentuximab vedotin (BV) has been tested as monotherapy and in combination in a variety of clinical settings, including in relapsed/refractory patients and as consolidative therapy following standard second-line therapy. Nivolumab and pembrolizumab, currently used in other malignancies that are known to utilise the programmed death pathway for survival, have shown outstanding results when used as single agents in heavily pre-treated (including BV refractory) patients. Individualising and adapting a patient's treatment course, whether augmenting or rationalising therapy, based on an interim positron emission tomography/computed tomography response is an important strategy currently under exploration to minimise toxicity while maximising response. Further work is needed to explore clinical and biological factors associated with improved outcomes. Knowledge of these factors combined with the movement of novel therapies into the front-line setting will enable individualised therapy to enhance clinical responses and minimise toxicities.

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Introduction

Classical Hodgkin lymphoma (HL) comprises approximately 10% (approximately 600 cases) of all new lymphoma diagnoses per year in Australia, and 30 000 cases globally. The affected population is bimodal in age distribution, with predominantly adolescents/young adults and, to a lesser extent, the elderly most commonly affected. Front-line treatment approaches vary with stage of disease (classified as 'early' and 'advanced') at diagnosis, but are essentially combination chemotherapy regimens, such as 'ABVD' and 'BEACOPP-escalated' with or without localised radiotherapy. For more detailed discussion, the reader is directed to the British Society of Haematology guidelines.[1]

Currently, approximately 75% of patients with HL can expect to enjoy long-term remission following first-line treatment. This is more likely among patients with favourable early stage disease and those that achieve complete remission (CR) early in their treatment. This cohort's excellent long-term survival unfortunately translates into significant increased risk of adverse effects following treatment (although incidence rates going forward will likely be reduced by the use of more sophisticated radiotherapy modalities). Side effects vary according to regimen, but include major morbidities, such as cardiopulmonary complications, stroke, fatigue and infertility, with secondary malignancies and cardiovascular disease being the two leading causes of death following treatment. Although the latency is 10–20 years,[2] the elevated risk of second cancers persists for 35 years or more after treatment, with a cumulative incidence of a second cancer of 48.5% at 40 years[3]; given the young age of onset and high survivorship, the disease burden caused by these complications is not insubstantial. Studies are investigating 'de-escalating' treatment, in an attempt to minimise long-term toxicity while still preserving good long-term remission rates. Successful de-escalation requires adoption of a risk-stratification strategy. Here, the challenge is to utilise blood/tissue and imaging biomarkers to predict accurately and monitor response to therapy.[4,5] Particular interest has focused on 18F-fluorodeoxyglucose positron emission tomography with computeted tomography (PET/CT). This imaging modality is now accepted as the preferred method of pre-treatment evaluation.[6] Interim PET/CT (i.e. performed between treatment cycles) may allow for risk-stratification to minimise over-treatment, while still achieving the same rate of remission and relapse-free survival.

The less fortunate grouping, a quarter of patients presenting with HL, are those that fail to achieve CR with first-line therapy or those that relapse (particularly within the first 12 months). For relapsed/refractory HL (RRHL), standard therapy consists of salvage chemotherapy (e.g. 'ICE' or 'DHAP') followed by high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). The 5-year overall survival rates are in the order of 55% for those with RRHL treated with ASCT, and lower again in those with adverse risk factors.[7] For patients who relapse after ASCT, reduced-intensity conditioning allogeneic stem cell transplantation (RIC-alloSCT) may provide a survival benefit for select patients with responsive disease. The merits of RIC-alloSCT are an area of active debate.[8] Although several studies indicate a likely graft-versus-lymphoma effect, nevertheless, many patients still experience a relapse of their disease.

Patients with RRHL represent a particular treatment challenge, as do older patients, who typically have poorer outcomes, are less likely to tolerate therapy and are poorly represented in clinical trials.[9] Here, there is an unmet clinical need for novel targeted therapies to enhance efficacy. This review will discuss recent advances in newly developed agents for HL and the emerging evidence for PET/CT-adapted therapy.

Anti-CD30 antibody therapies

Histopathologically, classical HL is characterised by the presence of Hodgkin (mononuclear) and/or Reed–Sternberg (multi-nuclear) (HRS) cells. These atypical B cells are collectively referred to as HRS cells.[10] Notably, HRS cells almost always express the cell-membrane tumour necrosis family receptor CD30, making this a prime therapeutic target. Brentuximab vedotin (BV, or Adcetris (Takeda Pharmaceutical Company U.S.A., Inc., Deerfield, IL, USA)) is an antibody–drug conjugate that selectively delivers monomethyl auristatin E, a cytotoxic antimicrotubule agent, into CD30-expressing cells[11] (Fig. 1).

Initially, BV as monotherapy (1.8 mg/kg 3-weekly up to 16 cycles) was evaluated in a Phase II setting in patients with RRHL.[12] All 102 patients had received at least two prior lines of intensive chemotherapy, including ASCT. Objective response was observed in 75% of patients, with almost half of these – 34% of the total cohort – achieving CR. Of particular note was the superior progression-free survival (PFS) achieved with BV; typically, successive therapies in multiply relapsed HL tend to result in progressive diminishing of PFS, however, estimated median PFS was improved with BV (8 months) compared with that achieved with the immediate prior line of therapy (if this was not ASCT (n = 57), 4 months). Longer term follow-up demonstrates the durability of response in those achieving CR.[13] Of the 34 patients achieving initial CR, 47%

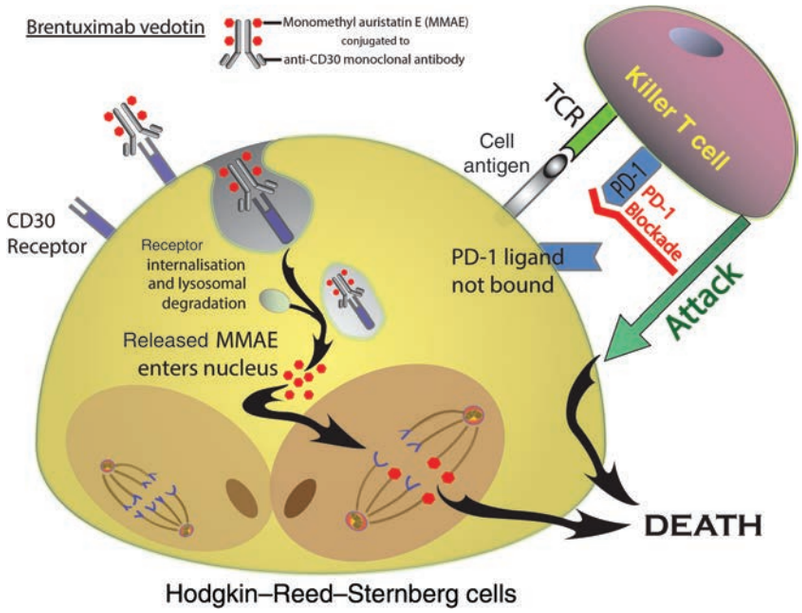

Figure 1 Mechanisms of action of novel agents. The anti-CD30 antibody component of brentuximab vedotin (an anti-CD30 antibody–drug conjugate) binds to the CD30 receptor on Hodgkin and Reed–Sternberg (HRS) cells, which then mediates endocytosis of the complex. After internalisation, monomethyl auristatin E is released through proteolytic cleavage and, when bound to tubulin, disrupts the microtubular network, inducing growth arrest and apoptosis. The binding of the PD-1 receptor to PD-1 ligands on HRS cells induces and maintains immune effector cell tolerance, enabling tumour cells to escape immune surveillance. By inhibiting this receptor, T-cell anti-Hodgkin lymphoma activity is restored.

remain in CR at a median follow-up of 53 months, with 16 of the 18 patients with durable remissions having achieved initial CR. Toxicity was manageable, with the most common treatment-related adverse events being peripheral (predominantly sensory) neuropathy, then nausea, fatigue, neutropenia and diarrhoea. A further observation was that salvage BV can be safely and effectively used as 'a bridge' to alloSCT.

The use of consolidative BV 4–6 weeks after ASCT was evaluated in the 'AETHERA' study.[14] This was the first Phase III placebo-controlled randomised study of maintenance therapy in patients with high-risk RRHL (defined as refractory to initial therapy, relapse occurring within 12 months, or relapse with extra-nodal involvement). A total of 329 patients was enrolled. Superior PFS was observed with the BV arm (43 vs 24 months), with consistent benefit across all subgroups, although adverse reactions led to treatment discontinuation in 32%. No survival benefit was seen in the relatively short follow-up provided, but this was confounded by the provision of BV to patients in the placebo group after progression. Indeed, when compared with historical survival data for high-risk patients with RRHL undergoing ASCT, the 3-year overall survival rate of 80% is remarkable and is consistent with clinical benefit of BV as both consolidation and rescue therapy. Interestingly, patients with PET/CT scan negativity prior to ASCT appeared to have reduced benefit. However, since PET/CT was not mandated and PET/CT evaluation criteria were not specified, interpretation is restricted. Further studies are required to elucidate better a population of patients most likely to benefit from BV maintenance after ASCT. These two pivotal studies led to BV's registration with the US Food and Drug Administration for use in RRHL and as maintenance therapy after ASCT. In Australia, it is currently approved by the Therapeutic Goods Agency, but at the time of writing remains unlicensed by the Pharmaceutical Benefits Scheme, and is only available on a compassionate access basis.

Regarding brentuximab as front-line therapy, a Phase I study of 51 patients with advanced HL[15] compared conventional ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) chemotherapy combined with 1.2 mg/kg BV (ABVD-Adcetris or 'ABVD-A'), against the same regimen without bleomycin (AVD-A). ABVD-A had an unacceptable rate of pulmonary toxicity (including two patient deaths), whereas no pulmonary side effects were seen with AVD-A, that is, concomitant administration of BV with bleomycin is contraindicated. Response rates between groups were almost identical (approximately 95%). These findings led to a large multi-centre randomised Phase III study (ECHELON-1) that is currently ongoing, comparing ABVD to AVD-A. An alternative to ABVD as the standard of care for advanced HL is BEACOPP-escalated (bleomycin, etoposide, doxorubicin, vincristine, procarbazine and prednisolone). This intensive regimen has superior PFS to ABVD in randomised studies,[16] however, opinion is divided as to whether the benefits the regimen brings in terms of disease control are sufficient to offset concerns over short- and longer-term toxicities, including secondary malignancies. A key

issue is that studies have not been statistically powered to test differences in overall survival. A network meta-analysis that included 10 111 patients with advanced stage HL showed an OS benefit of 10% at 5 years for BEACOPP-escalated over ABVD. Notably, regimens did not differ significantly with respect to second malignancies and leukaemia. Of interest, is the development of a new combination based on a modified BEACOPP backbone, with the substitution of BV for bleomycin and incorporating dacarbazine and dexamethasone (for procarbazine and prednisolone) and the loss of vincristine: 'BrECADD'. The intention is to minimise pulmonary, neurological, gonadal and infective toxicity, while maintaining efficacy. Recruitment is ongoing.

One alternative strategy to target CD30 is AFM13, a bispecific chimeric anti-CD30/CD16A antibody construct that unlike BV permits natural killer (NK) cell-mediated antibody-dependent cell-mediated cytotoxicity. Future studies are needed to establish AFM13's role in the management of HL.

Checkpoint blockade

Therapeutic developments have led to resurgent interest in cancer immunotherapy. In particular, blockade of the 'programmed death' PD-1/PD-L1/PD-L2 pathway has shown durable anti-tumour effects in a subset of patients with solid tumours. In this pathway, the PD-1 ligands (PD-L1 and PD-L2) engage the PD-1 receptor on T and NK cells, thus inducing and maintaining immune effector cell tolerance and allowing tumour cells to escape immune surveillance (Fig. 1).[17] There is an overexpression of PD-L1 and PD-L2 in the HRS cells of HL.[18] In some cases, this is due to chromosome 9p24.1 amplification that promotes PD-L1 induction through Janus kinase–signal transducer and activator of transcription signalling,[19] and in others, due to up-regulation mediated by Epstein–Barr virus (a virus that resides within HRS cells in a subset of cases[20]). Interestingly, HRS represent only approximately 2% of the diseased node,[10] the rest of the tumour microenvironment (TME) being composed of variable numbers of benign reactive cells, including immunosuppressive tumour-associated macrophages (M2 TAMS).[21] These cells are themselves enriched in PD-L1 and PD-L2,[22] demonstrating the importance of the TME in protecting the HRS cells from immunosurveillance. Blockade of the PD-1/PD-L1/PD-L2 axis potentiates T-cell anti-tumour activity.

In a ground-breaking Phase I study of 23 patients with RRHL, the anti-PD1 antibody nivolumab (Opdivo; Bristol-Myers Squibb, New York, NY, USA) was evaluated as monotherapy (3 mg/kg every 2 weeks for up to 2 years).[23] Patients were heavily pre-treated (87% of patients having had three or more prior systemic therapies and 78% having had prior ASCT), and 78% had relapsed following BV. Nivolumab was reasonably tolerated with adverse events, such as rash, pruritus and diarrhoea typically mild (Grades 1 and 2) and reversible, with five patients experiencing drug-related Grade 3 toxicity (no Grade 4 and 5 drug-related toxicities were reported). The objective response (using PET/CT) for a monotherapy in such poor-risk patients was remarkably high at 87% of patients, with 4 achieving CR and 16 partial response (PR). Among the 20 responders, 86% remained progression-free at 24 weeks. A similar study is ongoing for pembrolizumab (Keytruda; Merck, Kenilworth, NJ, USA). Early indicators from a Phase Ib trial are encouraging, with an overall response rate of 53% at 12 weeks.[24]

However, given the frequent aberrant expression of the $CD8^+$ T-cell antigen-presenting molecule β2M in the HRS cells of HL,[25] evidence for the mechanism of action of PD-1 blockade (e.g. by tumour antigen-specific $CD8^+$ T-cells) is not yet clear. Perhaps, part of the PD-1 blockade anti-tumour effect may be related to the blockade of reverse signalling through PD-L1, which has been described to impart a general anti-apoptotic cellular response.[26] Thus, not only is there a need to validate the clinical findings in controlled clinical trials, but it is imperative that such trials incorporate detailed correlative studies to provide a greater mechanistic understanding. This may in turn provide the scientific basis for developing more effective regimens. Also important will be the application of new checkpoint blockade strategies (such as anti-LAG-3) based on the unique features of the TME present in HL.[27]

Positron emission tomography with computed tomography-adapted therapy

Much work is currently underway with Phase III trials evaluating the role of mid-treatment restaging to enable effective tailoring of treatment to improve remission rates and minimise toxicities. This is being assessed in both advanced and early stage disease. Results of interim PET/CT appear to correlate well with long-term outcome following the treatment with ABVD.[28] In early stage disease, PET/CT-adapted therapy was trialled in the recently completed RAPID UK study,[29] with the aim of establishing non-inferiority of treatment de-escalation based on interim PET/CT performed after three cycles of ABVD. Patients with interim PET/CT-negative scans (426 of the 571 patients studied) were randomised to receive either standard radiotherapy or no further treatment (i.e. chemotherapy alone). Estimated 3-year PFS was 97% in the standard treatment

arm (i.e. treated with radiotherapy) compared with 90% in the de-escalation arm ($P = 0.02$). Non-inferiority of omission of radiotherapy in early stage HL was not established by this study (similarly in another large European study[30]). Two large Phase III trials by the German Hodgkin Study Group (HD16 and HD17) are currently underway, evaluating treatment de-escalation in patients with favourable and unfavourable early stage disease, respectively, with the omission of radiotherapy in PET/CT-negative disease following two cycles of ABVD for favourable disease and following two cycles each of ABVD and escalated BEACOPP in unfavourable disease.

Successful PET/CT-adapted therapy appears more feasible in advanced stage disease. This may be in part due to the excellent positive and negative predictive values of interim PET/CT for long-term disease outcome when performed after two cycles of ABVD, as well as the fact that there are still substantial improvements to be made with regards to progression-free and overall survivals in this population. The RATHL study is an international, Phase III randomised trial of risk-adapted therapy in 1137 patients with advanced stage HL.[31] Following two cycles of ABVD, those who were PET/CT-negative (85% of the total population) were randomised to either completing treatment with ABVD, as per current standard protocol, or having treatment de-escalated with the omission of Bleomycin. For those who were interim PET/CT-positive, treatment was intensified to a BEACOPP regimen with the aim of improving remission rates. Initial results have suggested a significant improvement in remission rates with dose intensification in interim PET/CT-positive patients, however, for reasons which are unclear, 3-year PFS results among PET-negative patients was a relatively disappointing 85%. The RATHL study involved centralised PET/CT review, with scan results being assigned according to the recently accepted Deauville five-point score (i.e. a semi-quantitative measure). In an exploratory NHMRC-funded sub-study of RATHL, the predictive value of metabolic tumour volume (a quantitative measure of the volume of tumour tissues with increased 2-deoxy-2[F-18] fluoro-D-glucose uptake) combined with circulating biomarkers is being assessed. If successful, approaches such as this may enable further refinement of risk-adapted therapy to be tested prospectively in future clinical trials.

Conclusion

The development of novel targeted therapies, with distinct modes of action and potentially non-overlapping toxicities, heralds a new era in the treatment of HL. While these novel therapies raise exciting possibilities, more work is required to establish their optimal role, either in combination with each other or with established treatments, such as chemotherapies and/or radiotherapies. This is a critical point, as it is unlikely that any one therapy/regimen will cure all patients. The challenge ahead will be to devise new strategies to identify particular subsets of patients, incorporating clinical and biological factors, with the highest likelihood of benefit to a particular therapy. This will permit individualised treatment with the aim of improving long-term outcome while minimising long-term treatment complications. This will only be achieved by greater engagement between industry, clinicians and scientists, and increased accrual into well-designed industry and investigator-led clinical trials.

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CLINICAL PERSPECTIVES

Lyme disease: why the controversy?

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Abstract

Some Australians have become convinced of the existence of locally acquired Lyme disease (LD). The history of LD, since its recognition in the early 1970s, is reviewed as a model for investigative approaches to unknown syndromes. Australian Management Guidelines for LD include the requirement for diagnostic testing by National Association of Testing Authorities-accredited laboratories using Therapeutic Goods Administration-licensed tests, which result in the efficient diagnosis of LD in overseas travellers. Despite this, patients who have not left Australia pay many thousands of dollars for non-specialist consultations and testing at overseas laboratories. Unproven long-term therapy with multiple antibiotics has resulted in serious complications, including allergies, line sepsis, pancreatitis and pseudomembranous colitis. Studies have shown that LD vectors are not found in Australia, and Lyme Borrelia has not been found in Australian vectors, animals or patients with autochthonous illnesses. I propose that (i) A non-controversial name for the chronic syndrome should be adopted, 'Australian Multisystem Disorder'. (ii) Research funding should enable the development of a consensus case definition and studies of the epidemiology of this syndrome with laboratory investigations to identify an aetiology and surrogate markers of disease. Prospective, randomised treatment studies could then be undertaken using ethical protocols.

Introduction

In recent years, some members of the Australian public have become convinced that they suffer from a protean illness that is a manifestation of locally acquired Lyme disease (LD) and that is becoming common in the community. Their efforts have resulted in enquiries by the Chief Medical Officer,[1] a report including a case study on tick-borne and Lyme-like diseases from the Australian House of Representatives[2] and another enquiry by the Australian Senate,[3] none of which was able to identify convincing proof of this condition. A total of 1265 submissions was received by the latter process, the majority of which were from individual patients or advocacy groups. A number of professional societies or clinicians cautioned against the assumption that LD is present in Australia. How can these disparate opinions be resolved? As medicine is not reliant on personal opinions, we should be guided by the documented history of LD written by the researchers who have preceded us.

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Epidemiology

In the early 1970s, it became clear that an epidemic of asymmetric, large joint oligoarthritis had appeared in eastern Connecticut.[4] A case definition was devised and enabled recognition of the epidemiological profile with peak incidence in summer and early autumn, with geographic clustering and an association with tick bites (*Ixodes dammini*, now *Ixodes scapularis*). Clinical studies described a characteristic preceding skin lesion (erythaema chronicum migrans (ECM))[5] and the propensity for a resolving/relapsing course. Traditional tests for the causes of inflammatory arthritis were negative in these cases.

Diagnostics/pathogenesis

Initial attempts to culture an organism from ticks or patients were unsuccessful, but Burgdorfer's group eventually isolated a spirochaete (subsequently named *Borrelia burgdorferi*) from *I. dammini*, which bound to immunoglobulins from LD patients.[6] The analysis of ticks from an island with high LD prevalence (Shelter Island) demonstrated an arthropod infection rate of 61%.

Infection with the putative pathogen in rabbits on which *I. dammini* had fed produced characteristic ECM lesions. These organisms were used in an indirect immunofluorescence assay, which demonstrated the development of high titre-specific antibodies in these infected rabbits. The same assay detected specific antibodies in the serum of patients with clinically diagnosed LD, suggesting that the tick spirochaete was the same organism as the agent of LD.[7] The availability of a diagnostic laboratory test then enabled the clinical spectrum of infection to be further defined to include late neurological and cardiac abnormalities.[8,9] Subsequent technological advances enabled the development of diagnostic molecular tests, which were shown to be more sensitive than cultures.[10] Molecular epidemiology of human isolates of Lyme Borrelia (LB) has clarified the global prevalence of the *B. burgdorferi* sensu lato complex, which now also includes Europe (*B. burgdorferi* sensu stricto (ss), *Borrelia afzelii* and *Borrelia garinii*), eastern Russia (*B. burgdorferi* ss, *B. afzelii* and *B. garinii*), China (*B. afzelii* and *B. garinii*), Japan (*B. afzelii* and *B. garinii*),[11] South Korea (*B. afzelii*)[12] and Taiwan (*B. burgdorferi* ss, *B. afzelii* and *B. garinii*)[13] and extends into South America (*B. burgdorferi* ss, *Borrelia chilensis* and *B. garinii*).[14]

In areas known to be endemic for LD, diagnosis is predominantly through 'two-tiered' serology with enzyme immunoassay (EIA) and immunoblot.[15] This confirms exposure which, when combined with a typical clinical syndrome (i.e. ECM, acrodermatitis, lymphocytoma, joint swelling, Bell's palsy, radiculoneuropathy, lymphocytic meningitis, encephalitis, heart block) occurring in a patient in an endemic region, can be considered sufficient for the initiation of treatment. In areas not known to be endemic for LD, other causes of ECM exist[16–18] (which should be ruled out), or serology may not be sufficiently specific.[19] Conclusive evidence for LD should only be obtained by culture or molecular methods in such regions. The discovery of a new endemic area should also be confirmed by additional independent researchers. This is the rationale behind the Australian Management Guidelines, which includes the requirement for diagnostic testing in National Association of Testing Authorities (NATA)-accredited laboratories using Therapeutic Goods Administration of the Australian Government (TGA)-licensed tests.[20] The diagnostic work-up should preferably include protocols that can also identify other agents known to be transmitted by tick bites in Australia.[21,22]

Life cycle

Further studies were able to define the complex zoonotic life cycle of LB in North America[23] and Europe[24] and the critical role that vectors and reservoir hosts play in effective transmission cycles.[25] For example, some regions have less efficient vector ticks, which result in lower prevalence rates,[26] and the presence of a suitable vector does not necessarily imply that LB are also present.[27] The detection of LB in ticks may not be relevant for human disease as some infected ticks are not efficient vectors for transmission.[28] In addition, the expansion of reservoir host numbers dramatically increases the prevalence of LD in some areas.[29] It is expected that climate change will also increase the geographical distribution and/or local prevalence rates.[30] The vectors of LD are generally Ixodid ticks, including *I. scapularis*, *I. pacificus*, *I. ricinus* and *I. persulcatus*.[31]

Treatments

The identification of the LD pathogen enabled the discovery of an effective antibiotic regimen.[32] Controlled clinical trials demonstrated that the majority of patients could be cured with short-term monotherapy with an oral antibiotic.[33,34] Neurological manifestations, aside from facial palsy, should be managed with intravenous therapy.[35] Co-infection with other arthropod-borne pathogens was recognised and may complicate the diagnosis and treatment.[36]

Delayed complications of LD have been described (now called 'post-treatment Lyme disease syndrome'), which are characterised by symptoms of fibromyalgia[37] or chronic fatigue.[38] Investigations in such cases did not reveal any evidence of active infections. Other ill-defined cases of non-specific symptoms have been ascribed to 'chronic Lyme' without proof of active infection.[39] It is recommended that clinicians abstain from testing for LB unless the patient has epidemiological risks or compelling clinical signs.[40] Unnecessary laboratory testing is not only prone to inaccurate diagnoses but also places undue burden on health systems.[41] Controlled trials of antibiotic treatment of these chronic syndromes did not reveal any beneficial effect.[42,43] It was concluded that post-treatment Lyme cases may be a manifestation of immunological processes or an ill-defined post-infectious syndrome[44] and that such cases should not be treated with antibiotics.[45] Nevertheless, non-scientific treatments using multiple antibiotics for many years have been increasingly utilised. Such treatments may have serious, even fatal, effects and are expensive.[46–50] Australian experiences include patients paying many thousands of dollars for non-specialist consultations and transportation of specimens for testing at overseas laboratories using non-approved protocols that have resulted in misdiagnoses associated with experimental treatments, which have caused serious complications, including line sepsis, pancreatitis and pseudomembranous colitis

(reported through the national ASID-OzBug bulletin board). Most testing in fully accredited Australian laboratories using TGA-licensed assays are associated with no out-of-pocket expenses, so patients tested outside of this system are burdened with crippling costs for no benefit. This is an example of modern societal environments hindering the proper scientific evaluation of 'medically unexplained symptom syndromes'.[51]

Australian data

Studies commencing in 1988 (and which included ECM cultures) have not demonstrated the presence of LB in non-peripatetic Australians, reservoir hosts (17 marsupials) or tick vectors (12 000 analysed by microscopy and culture and 1000 by polymerase chain reaction).[52] There have been some tantalising clinical diagnoses[53] reported (which may be confounded by a high incidence of local allergic reactions to *I. holocyclus* bites[52]). Serological studies have not been diagnostic; a 1.8% screening seropositivity rate was reported in 4372 patients with negative immunoblot assays, with no difference in the prevalence between high- and low-risk patients.[53] False-positive serological reactions were also documented in 24 patients with other infections or autoimmune disease.[54] Australian diagnostic laboratories have diagnosed cases of imported LD (including by culture).[54] A single, non-accredited laboratory has reported five polymerase chain reaction-positive ECM specimens.[55,56] There is doubt over those reports because of the lack of supporting sequencing data, concerns of non-specific amplification and the lack of confirmation by an independent laboratory.[53] A more recent study has confirmed the absence of LB in Australian ticks (196 *I. holocyclus*).[57] The specific vectors of bona fide LD described above[58] are not found in this country, but our most common Ixodid tick appears to be incapable of LB transmission.[59] It would be surprising to find LB in Australian ticks as this continent separated from Gondwanaland 150–200 million years ago, and the intimate life cycles of the participants in LD of Europe and America are likely to have been established after that tectonic shift.[60] Another marker of autochthonous LD is the dog (*Canis lupus familiaris*), which is exposed to appropriate vectors common to their human companions. A study in 2015 of 385 dogs found a screening EIA seropositive rate of 20.3%, which was no higher in 'at risk' dogs (38.1% in 84 animals fed to *I. holocyclus* to raise anti-tick antibodies) than in 'no risk' control dogs (30% in 30 animals), and none was confirmed by immunoblot apart from two vaccinated animals that were imported from the US (P. Irwin, pers. comm., 2016).

In summary, LD vectors are not found in Australia, and LB has not been found in Australian vectors, animals or patients with autochthonous illnesses. The data above show that countries with demonstrated endemic LD have no trouble in demonstrating the presence of LB in vectors, reservoirs or patients. This would argue strongly against the presence of LD in Australia.

Frequently asked questions

What is the mysterious illness experienced in Australian patients?

This is not currently clear, and it is far from certain that they are a homogenous clinical population. A uniform case definition should be developed by relevant health jurisdictions after consultation with expert groups. Data should then be collected to determine the prevalence of this condition, and periodic surveys would be able to conclude if the incidence is rising over time.

How should such patients be diagnosed?

It is recommended that patients who do not fulfil the case definition for LD, especially if they have not left Australia, should not be tested for LB. Alternative causes of rheumatological disease or fatigue syndromes and other infectious agents known to be transmitted by tick bites in Australia[21,22] should also be excluded. In the meantime, symptomatic treatment, including psychological support, should be offered.[39]

Should diagnostic specimens be sent out of Australia to be tested by overseas laboratories (at enormous cost)?

No. There is no evidence that bona fide LD cases are being missed by licensed Australian laboratories. Our laboratories operate to the highest standards, usually at a level above those at which pathology tourism laboratories operate. Non-NATA-accredited laboratories within Australia are also not licensed to test diagnostic specimens and should not be used for LD testing of humans.

Should patients receive empirical multi-drug therapies for years?

No. The first principle of medicine is non-maleficence, that is, 'primum non nocere' (probably Hippocrates, but first documented by Sydenham). These non-scientific empirical protocols have not been proven to be efficacious by randomised controlled prospective treatment trials. They have been shown to have the potential for serious, even fatal, adverse effects and are extremely expensive for desperate patients to afford. Their use should only be

offered as part of an experimental protocol after informed consent has been obtained, at no cost to the patient.

What is the best way forward?

1 A non-controversial name for the syndrome should be adopted (and it should not contain the name Lyme); perhaps Australian Multisystem Disorder would be appropriate.
2 Development of a consensus case definition should enable characterisation of the epidemiology of the syndrome. It appears that the most common symptoms include fatigue, joint and muscle pain and features of neurocognitive impairment.[61]
3 Once a case definition has identified a coherent group of patients with similar symptoms and signs, studies should be undertaken to identify common risk factors, including specific exposures, to determine if a characteristic transmission profile exists. Once this is achieved, high-risk or symptomatic patients should be asked to consent to have specimens collected (blood, tissue, attached arthropods, even cerebrospinal fluid if required as part of routine clinical investigations). Case ascertainment should then be undertaken and baseline characteristics documented using objective and reliable research tools administered by an experienced team of professionals and performed by NATA-accredited laboratories using TGA-licensed assays according to accepted international protocols.
4 If the epidemiology or initial pathology identified candidate pathogens, patients could be invited to enrol in prospective, randomised treatment studies after giving informed consent. Such research should be undertaken by a multidisciplinary team, which includes Infectious Diseases specialists experienced in managing Borrelioses in endemic regions.

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ETHICS IN MEDICINE

Legal and ethical issues associated with Advance Care Directives in an Australian context

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Abstract

The need for appropriate mechanisms guiding end-of-life care is increasingly vital. This commentary compares the use of Advance Care Directives (ACD) in New South Wales and South Australia in order to highlight the inconsistency in Australian legislation, before exploring common problems, legal concerns and ethical issues associated with their application in an adult population. The benefits and detriments of statutory legislation for ACD are also evaluated.

Introduction

An Advance Care Directive (ACD), or living will, is a document outlining an individual's wishes regarding future refusal or acceptance of medical care should they lose decision-making capacity.[1] In the context of advances in life-prolonging technology, and the ageing of our population with an increase in associated multiple comorbidities, the need for appropriate mechanisms guiding end-of-life care is increasingly vital. These mechanisms are not necessarily well understood by health professionals. This commentary compares the use of ACD in New South Wales (NSW) and South Australia (SA), before exploring common problems, legal concerns and ethical issues associated with their application in an adult population. NSW and SA were selected for comparison because of the significant

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differences in the legal standing of ACD in each of these states, highlighting the inconsistency in Australian legislation. Finally, the benefits and detriments of statutory legislation for ACD are evaluated.

The use of Advance Care Directives in Australia: a comparison of South Australia and New South Wales

Although the legal standing of ACD varies between Australian states, there are various basic commonalities. A competent adult can create a written directive and/or assign a substitute decision-maker (SDM) to make proxy judgements in his/her place. ACD are just one element of advance care planning.[2] They can cover many health issues but often outline situations in which life-sustaining measures such as mechanical ventilation, cardiopulmonary resuscitation or artificial hydration and nutrition are considered acceptable or unacceptable.[3]

Living wills can request that all appropriate active treatment be undertaken. They cannot, however, demand treatment not offered to manage a condition in accordance with good medical practice or request an illegal alternative, such as euthanasia.[4]

The differences in ACD legislation across Australia can be highlighted by comparing NSW with SA. The legal status of ACD in NSW is governed by common law,[1,5] which is case law that has been developed on the basis of preceding rulings by judges and courts. According to the Supreme Court of NSW, an ACD must be respected if it is 'made by a capable adult, and it is clear and unambiguous, and extends to the situation at hand'.[5] In SA, the legal status of ACD is governed by statutory law, which is a form of written law passed by legislature and government. Statutory law tends to be less flexible than common law. Living wills are legally binding under the ACDs Act 2013 in SA.[6]

There are no mandatory forms in NSW, with an oral dictation, letter or other written document being acceptable.[1,5] In contrast, SA has a specific form that individuals must complete if they wish for their ACD to be legally binding.[6] A witness is advised in NSW, but is mandatory in SA, and must not be a beneficiary in the ACD author's will, SDM, medical practitioner or paid carer.[1,6] In SA, a 'binding provision' must be followed. This provision sets out a refusal of a particular medical care in a specific circumstance.[6]

Conflicts regarding the content or application of an ACD can be resolved by seeking legal advice, and in NSW the NSW Civil and Administrative Tribunal Guardianship Division may be consulted. In SA, a Public Advocate is consulted first, and the decision may be referred to the Guardianship Board of SA.[6]

Common problems with Advance Care Directives

There are several problems with living wills. Firstly, the proportion of Australian adults with an ACD is decidedly low, with estimates ranging from <1 to 12.5%.[7–9] Proposed explanations for this include lack of awareness and an aversion towards discussing end-of-life issues.[7,9]

Even if a living will *has* been created, accessibility can be difficult, because either treating physicians or family members are unaware the document exists or cannot locate it when required.[10,11] In an acute emergency, if a clinician has no knowledge of treatment objections, urgent medical care can be provided without gaining consent.[1]

Moreover, ACD are rarely specific enough to offer unambiguous directions in all clinical situations.[12] If a living will does not provide instructions reflecting the medical scenario that actually occurs, it may be virtually useless.[4] Alternatively, if the ACD has some, but not complete, clinical relevance, it may make the task of interpreting the patient's wishes even more difficult. For example, does an individual refusing ventilation intend this only to apply if it will be a longer-term measure, rather than, say, a temporary intervention following an acute, potentially reversible illness? The situation is complicated further because most patients lack complete understanding of the subtleties of all treatment options.[11] Unclear terminology adds additional uncertainty. For example, is artificial feeding considered 'extraordinary care'? What exactly constitutes a 'meaningful quality of life'? Relevant stakeholders may interpret ambiguous terminology differently, creating confusion and conflict while obscuring the patients' true beliefs.[13]

Furthermore, people's preferences change over time. If they have not updated their ACD, it may not accurately reflect their wishes. The advent of new technology further compounds this, as individuals cannot have accounted for novel treatment options.[10]

Finally, confusion about the legality of ACD is rife, particularly in NSW and Tasmania where no statute exists. Lack of clarity regarding legal protection makes many clinicians reluctant to follow ACD if even slight doubt about their applicability exists. Inconsistent nationwide legislation amplifies this problem, creating questions about the currency of interstate ACD.[4,10]

Competency and validity

Under both common and statutory law, an ACD is considered valid if it is written by a competent author without undue influence of others.[13] Yet there are also

various other factors influencing validity that can be used to legally overturn an ACD.[1,14–16] These are summarised in Table 1.

Competency is an individual's decision-making capacity, encompassing his or her ability to understand the nature and effects of treatment options.[17] For adults (i.e. person older than 18 years) to be considered competent, individuals must be able to understand and retain the information provided to them about their illness, therapy options and the consequences of consenting to or refusing treatment. They must be able to weigh up this information, come to a decision and communicate their choices.[18]

Loss of competency is required for an ACD to come into effect. This loss may be permanent, temporary or fluctuating, meaning it should be assessed at the time of each decision. The level of capacity required is proportionate to the decision at hand, and capacity is always presumed unless proven otherwise.[19,20]

Capacity can be assessed by a legal or medical practitioner. There is no set test, but the Attorney General's Department of NSW suggests a series of questions in their 'Capacity Toolkit'.[21] Evaluating capacity should include assessment of global cognitive function and, more specifically, functional decision-making, including whether a patient can describe the information in his/her own words.[22] Tests for competence assess decision-making *capacity*, not whether a decision in itself is logical.

Ethical and legal issues for patients, families and clinicians

The moral underpinning of the ACD is the notion of autonomy.[15,16] Everyone has the right to make decisions regarding their healthcare, an ethical principle which exists at the heart of modern medicine.[23] Allowing competent adults to specify preferences to be enacted when their capacity is lost protects their self-determination during a state of powerlessness. Living wills are also important in stimulating in-depth discussions about medical preferences extending beyond the creation of the document itself, a vital step forward given the discomfort associated with the topic of end-of-life care.[24]

However, ethical questions arise when considering whether an individual can predict his or her future wishes, casting doubt on whether ACD actually promote autonomy. According to Dworkin,[25] 'people are not the best judges of what their own interests would be under circumstances they have never encountered and in which their preferences and desires may have drastically changed'. When patients lose competence, they also surrender the ability to re-evaluate their previously stated instructions in light of the specific circumstance at hand. We cannot truly consider this to be 'informed consent'.[26] How can we be certain patients' wishes remain unchanged when they themselves can no longer understand them?

This issue can be further explored by examining the case of dementia. Competence is lost slowly over years. During this time, the individual still experiences pleasure and pain but his/her memory, personality and behaviour may change. This raises the notion of personhood, questioning whether the apparent lack of psychological continuity renders an advanced dementia patient and his or her former self two different people.[27] Many argue that individuals' critical interests, those derived from their values and beliefs, are more enduring than their experiential interests, which encompass the activities they take pleasure in, as the latter may be altered by dementia.[16,25,28] Given that critical interests form the basis of an ACD, it would, therefore, be ethically justifiable to consider written directions as an extension of the incompetent patient's self-determination.

However, there is ongoing debate regarding the relative importance of critical and experiential interests, and it is thus vital that their role in advance care planning is

Table 1 Factors influencing the validity of an Advance Care Directive (ACD)

Factors that can render an ACD invalid	Factors that cannot be used to render an ACD invalid
• The author was not competent at the time it was created. • It was created under duress. • It no longer reflects the wishes of the author. • It was not intended to apply to the clinical situation at hand. • It is too ambiguous to enable a clear interpretation. • New treatment options have arisen that were not available when the ACD was written but could have influenced the author's decision. • It has not been signed by an appropriate witness.†	• The decisions in the ACD appear illogical to doctors, family or friends. • The decisions in the ACD conflict with the values of doctors, family or friends.

†This criterion applies only in states such as South Australia that have statutory law that necessitates a witness.

not oversimplified.[26] Moreover, although some believe that precedent autonomy in the form of an ACD is ultimately the best approximation we have of an incompetent individual's wishes,[25] there is also little evidence that ACD accurately predict future preferences.[26,29]

Advance Care Directives are often touted as morally worthwhile because they can offer patients a sense of control over an unpredictable, distressing situation, providing a chance to die with dignity.[30] While this is true to a certain extent, it must also be recognised that patients do not necessarily want complete control over decisions made after they have lost competence. A number of studies have found that most patients would prefer to give their SDM at least some leeway in decision-making, rather than strictly adhering to their documented wishes.[30–34] Unlike the patients themselves, SDM have the ability to evaluate the benefits and burdens of treatment in relation to the circumstance at hand, making informed choices in the context of both the patient's stated values and best interests.

Furthermore, it has been proposed that fear of a 'dictatorial' approach to ACD, whereby SDM have no legal or ethical room to override the outlined wishes, may be one of the reasons for the low ownership of these documents.[32] While ACD are still valuable in providing documentation of a patient's preferences, it is important for advance care planning to involve discussion about and documentation of how a patient would like decisions to be made, rather than focusing solely on what those decisions might be.[33,34]

Another argument supporting the use of ACD is that they can minimise guilt about leaving family with such demanding decisions.[24] A systematic review conducted by Wendler and Rid in 2011 found that while the evidence is often ambiguous, at least one third of SDM experience significant emotional burden as a result of having to make decisions for their loved ones.[35] However, Wendler and Rid also found that having an ACD was commonly linked to a more positive experience for SDM, giving them more confidence as to the patient's preferences.[35] Even a vague ACD provides a starting point for discussion by showcasing documented evidence of a patient's values, relieving some of the burden of decision-making.[36] An ACD can help relatives feel more morally comfortable ceasing life support or limiting other extraordinary measures, rather than feeling complicit in their loved one's death.

Ideally, an ACD satisfies the moral duty of doctors and family to promote beneficence and non-maleficence. Respect for autonomy and the aforementioned psychosocial benefits fulfil a patient's best interests while harm is avoided by discouraging over-treatment and under-treatment.[29,37] In reality, however, this is not often the case. While advance care planning as a whole has been associated with a 40–80% reduction in hospitalisation rates and triple the number of palliative care referrals,[29] there is little evidence that ACD lead to improvement in the accuracy of surrogate decisions.[26]

Furthermore, ethical and legal dilemmas arise when an ACD contradicts a patient's best medical interests. Legally, the document must be followed in accordance with good medical practice unless it is proven to be invalid, or a physician risks facing criminal or civil liability, which may include battery and assault charges.[1,6] For example, if a patient completely refuses blood transfusion, this wish must be respected, even if it proves fatal. This can represent a significant moral quandary for doctors, as the medical profession highly values the sanctity of life.[15] On the other hand, having patients' wishes documented makes it easier for physicians ethically to justify ceasing treatment, even if it means contradicting their inherent desire to preserve life. An ACD also offers legal protection should the document be followed with good intention.[6]

Problems also arise when family members do not want an ACD followed. This can stem from disagreements regarding treatment utility and interpretation of the ACD, or be influenced by cultural views on the communal nature of decision-making.[1] Ultimately, it is the legal and moral responsibility of an SDM to act in accordance with patients' wishes, even if this means going against their own personal values. If no agreement is reached after extensive discussions with the healthcare team, the case can be referred to relevant authorities for external evaluation.[6]

Arguments for and against legislation for Advance Care Directives

The main argument against legislating for ACD is that statutory law is inflexible. This lack of leeway for case-by-case evaluation can lead to a failure to balance patient autonomy with the need to ensure these wishes are not inappropriately applied.[14] Furthermore, legislation for ACD usually mandates one specific form. This limits an individual's freedom of expression and can unnecessarily render an ACD invalid merely due to bureaucracy.[14] Moreover, it could be argued that more formalised laws place even well-intentioned physicians at increased risk of legal liability.[38]

However, enshrining ACD in statute is beneficial in creating more clarity and consistency, particularly if this legislation applies nationwide.[4] This can improve understanding of ACD among all stakeholders, maximising the effectiveness of their application, increasing the likelihood that physicians will promote their use and improving uptake among patients. Legislation also provides more protection for doctors and offers greater certainty that

autonomy will be respected, instilling more confidence in patients and thus increasing uptake rates.[38] Furthermore, well-constructed, nationally uniform legislation can minimise problems with ACD usage. For example, it could increase accessibility through a standardised register for all ACD or provide a formal mechanism to update healthcare preferences so as to encourage people to do so regularly.[39]

Overall, the benefits of legislation outweigh any detriments, allowing the positive potential of ACD to be more fully realised.

Conclusions

Advance Care Directives are an imperfect answer to a multifaceted ethical and legal question. However, particularly when used in the context of broader advance care planning, they are ultimately the best solution that we currently have available. The capacity for ACD to promote autonomy is a subject of ongoing debate, and there is little evidence that these documents tangibly improve the accuracy of surrogate decisions. Yet for patients, families and doctors, ACD provide an important starting point for discussion around end-of-life decisions, allow patients to express their wishes regarding not only treatment preferences but also the freedom they would like afforded to their SDM, and may reduce the burden of decision-making. Creating clear statutory legislation to govern their use is an important step towards maximising their effectiveness.

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ORIGINAL ARTICLES

Prevalence and prognosis of hypoglycaemia in patients receiving maintenance dialysis

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Key words
hypoglycaemia, end-stage renal disease, mortality.

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Abstract

Background: End-stage renal disease is a common predisposing condition for the development of hypoglycaemia.
Aim: To determine the effect of hypoglycaemia on the mortality of patients undergoing maintenance dialysis.
Methods: Retrospective and descriptive analyses were performed in five dialysis centres in the Republic of Korea between June 2002 and August 2008. We enrolled 1685 patients who had undergone dialysis for at least 1 month.
Results: We identified 453 episodes of hypoglycaemia in 256 of 1685 patients (15.2%); 189 patients (73.8%) had diabetes, whereas the other patients did not. The occurrence of hypoglycaemia in patients receiving dialysis appeared to be a life-threatening complication because 27.0% of patients died within two days of the onset of a hypoglycaemic episode. Older age, low serum albumin levels and infections were independent risk factors for total mortality in these patients. Furthermore, the absence of diabetes, age and serum glucose levels were independent factors associated with early mortality within two days of the development of hypoglycaemia.
Conclusion: Although several factors were associated with mortality, the degree of hypoglycaemia, absence of diabetes and old age were associated with early mortality. Elderly hypoglycaemic patients, especially those without diabetes, should be closely monitored.

Introduction

Patients with end-stage renal disease (ESRD) and diabetes are not only insulin-resistant but also prone to hypoglycaemia because of impaired renal gluconeogenesis, malnutrition, altered pharmacokinetics of insulin and hypoglycaemic agents.[1,2] Chronic complications of diabetes result from hyperglycaemia, but hypoglycaemia is an additional component of morbidity and mortality.[3–6] Patients undergoing haemodialysis are at a high risk of cardiovascular mortality, and hypoglycaemia is fatal in the presence of cardiovascular disease.[4,7]

*These authors contributed equally to this paper.

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In addition, ESRD causes disturbances of glucose homeostasis in non-diabetic as well as diabetic patients.[8] The mechanism has not been established, but the disturbances have a multifactorial aetiology, including chronic uraemia, anorexia, metabolic acidosis and changes in concentrations of growth hormone and glucagon.[8,9]

Although the risk of hypoglycaemia could be reduced by the use of glucose-supplemented dialysis fluids, glycaemic patterns are barely predictable, making it difficult to control blood glucose levels without the risk of hypoglycaemia in patients receiving haemodialysis.[10,11] A previous study on patients undergoing haemodialysis or peritoneal dialysis reported that 3.6% of hospitalised patients with ESRD had hypoglycaemia.[1] We conducted this study to determine the effect of hypoglycaemia on the mortality in patients with ESRD undergoing chronic dialysis.

Methods

Patients

Retrospective and descriptive analyses were performed at five dialysis centres of Hallym University Medical Center in Korea between 1 June 2002 and 31 August 2008. We enrolled patients with ESRD who underwent haemodialysis or peritoneal dialysis for at least one month. With the approval of the institutional review board at each participating site, we collected the electronic files containing the medical records of the enrolled patients. The study population included patients with ESRD aged 18 years or older with and without diabetes. Patients with acute renal failure or kidney transplantation and those not receiving dialysis at the time of the diagnosis of hypoglycaemia were excluded from the study. Cases of hypoglycaemia diagnosed by home blood sugar monitoring devices (glucometers) were not included.

Measurements and outcomes

The electronic medical charts were queried using the Refomax Dataware System (Samsung SDS, 2002, Seoul, Korea). Clinical data, including age, gender, diagnoses, clinical conditions, nutritional status, numbers of insulin and hypoglycaemic drug orders, numbers of hypoglycaemic episodes, any complications and survival status, were obtained and analysed. Any diagnosis, condition or therapy found to be associated with hypoglycaemia in our patients was defined as a risk factor for the condition. Hypoglycaemia was defined as a serum glucose level of <2.8 mmol/L. In hospitalised patients, the serum glucose levels were generally measured at 06:00 and as required thereafter. In patients receiving maintenance haemodialysis, blood samples were also drawn immediately after the insertion of the access needle and as required thereafter. We used a dialysate glucose concentration of 100 mg/dL regardless of diabetes. Malnutrition was defined by a serum albumin level <25 mg/L, continuous decline in dry weight, body weight less than 70% of ideal weight or a chart notation of cachexia. Serum glucose and biochemical parameters were measured using a Hitachi 7600 autoanalyser (Tokyo, Japan). Total mortality was defined as death from any cause occurring within one year of the development of hypoglycaemia. Early mortality was defined as death within the first two days of the development of hypoglycaemia.

Statistical analysis

Results are expressed as the mean ± standard deviation. A two-sample Student's *t*-test was used to compare mean differences in age, haemoglobin level and serum levels of glucose, albumin, phosphate and creatinine. We used the Mann–Whitney nonparametric U test to assess any differences in serum glucose levels. Differences in proportions were assessed using the chi-squared test. Stepwise multivariate logistic regression analysis was performed for all variables showing significance in an initial univariate analysis. Results are presented as odds ratios (OR) and 95% confidence intervals (CI). Differences were considered statistically significant for a two-sided test at $P < 0.05$. Data were recorded using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), and statistical analyses were conducted using the SAS software package (version 6.10, SAS Institute, Cary, NC, USA).

Results

Among the 1685 patients receiving dialysis (1176 with haemodialysis; 509 with peritoneal dialysis), 256 had documented hypoglycaemia (453 episodes), an incidence of 15.2%. Multiple episodes of hypoglycaemia occurred in 84 patients (32.8%). Of the 256 patients, 132 were male, and 124 were female. The mean age of the patients was 62.4 ± 12.4 years (range 19–89).

A total of 189 patients (73.8%) had diabetes, whereas the other patients did not. The incidence of hypoglycaemia was 21.6% in patients with diabetes and 8.5% in patients without it ($P < 0.001$). The basic characteristics and results of biochemical of tests of the hypoglycaemic patients according to the presence or absence of diabetes are summarised in Table 1. Patients with diabetes were older ($P = 0.001$), had shorter durations of dialysis ($P < 0.001$), lower serum albumin levels ($P = 0.01$) and

Table 1 General characteristics of hypoglycaemic patients with and without diabetes mellitus†

Characteristics	DM (n = 189)	Non (n = 67)	P
Age (years)	64.1 ± 10.9	57.6 ± 14.7	0.001
Female gender (%)	92 (48.7)	32 (47.8)	1.00
History of cardiovascular disease (%)	95 (50.3)	20 (29.9)	0.004
Hemodialysis (%)	135 (71.4)	51 (76.1)	0.53
Duration of dialysis (months)	35.3 ± 35.8	59.5 ± 44.3	<0.001
Glucose (mmol/L)	1.94 ± 0.58	1.94 ± 0.71	0.95
Hemoglobin (g/L)	99 ± 16	101 ± 14	0.30
Calcium (mmol/L)	2.1 ± 0.2	2.2 ± 0.3	0.14
Phosphorus (mmol/L)	1.9 ± 0.9	2.0 ± 0.8	0.49
Hb_{A1c} (%)	7.3 ± 2.1	5.3 ± 1.1	0.006
Albumin (g/L)	31 ± 7	34 ± 7	0.01
BUN (mmol/L)	16.2 ± 8.0	19.5 ± 10.1	0.02
Creatinine (μmol/L)	539.2 ± 247.5	733.7 ± 459.7	0.002
Mortality (%)	64 (33.9)	22 (32.8)	1.00

†Results are presented either as means ± standard deviation or as n (%) with n = number of patients and % = percentage of patients in the group. BUN, blood urea nitrogen; DM, diabetes mellitus.

Table 2 Risk factors associated with hypoglycaemia†

Risk factor	DM (n = 189)	Non-DM (n = 67)
Drugs	179 (94.7)	37 (55.2)
Insulin therapy	140 (74.1)	1 (1.5)
Oral hypoglycaemic agent	44 (23.3)	0 (0)
Beta blocker	57 (30.2)	17 (25.4)
ACEI/ARB	133 (70.4)	32 (47.8)
Malnutrition	33 (17.5)	7 (10.4)
Infection	47 (24.9)	21 (31.3)
Liver disease	5 (2.6)	1 (1.5)
Hyperkalemia therapy	1 (0.5)	2 (3.0)
Malignancy	0 (0)	3 (4.5)
Shock	3 (1.6)	3 (4.5)

†Results are presented either as means ± standard deviation or as n (%) with n = number of patients and % = percentage of patients in the group. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; DM, diabetes mellitus.

a higher frequency of cardiovascular disease ($P < 0.001$) than patients without diabetes.

A total of 186 patients (72.7%) was receiving haemodialysis, and 70 (27.3%) were treated with peritoneal dialysis. The incidences of hypoglycaemia in patients receiving haemodialysis (15.8%) and those receiving peritoneal dialysis (13.8%) did not differ significantly. The basic characteristics and biochemical test results of the hypoglycaemic patients classified according to the dialysis method were similar. However, patients receiving haemodialysis had higher levels of serum albumin (33 ± 7 vs 29 ± 6 g/L; $P < 0.001$) than those receiving peritoneal dialysis (Table S1, Supporting information).

We identified a number of risk factors associated with hypoglycaemia (Table 2). A total of 95 patients (37.1%) had more than one risk factor for hypoglycaemia. Insulin therapy (74.1% of patients with diabetes) was the most common risk factor for hypoglycaemia in patients receiving dialysis. A total of 44 patients (23.3% of those with diabetes) was treated with oral hypoglycaemic agents (33 with sulfonylureas, 7 with meglitinides, 3 with thiazolidinediones and 3 with alpha-glucosidase inhibitors). Medical histories revealed that many patients received other drugs associated with hypoglycaemia (74 with beta-blockers and 165 with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers).

A total of 40 (15.6%) of the hypoglycaemic patients had clinical malnutrition, and 68 (26.6%) showed evidence of infections (26 with pneumonia, 15 with wound infections, 13 with peritonitis, 4 with vascular access infections, 2 with hepatobiliary infections and 8 with other infections). Methicillin-resistant *Staphylococcus aureus* (n = 12) was the most common infecting microorganism, followed by *Streptococcus spp.* (n = 6), *Klebsiella spp.* (n = 6), *Enterococcus spp.* (n = 5), *Escherichia coli* (n = 4), methicillin-sensitive *S. aureus* (n = 3) and *Mycobacterium tuberculosis* (n = 3). The incidences of hepatitis B and hepatitis C infections were 4.3% (n = 11 patients) and 3.1% (n = 8) respectively. Five patients (2.0%) had hepatic cirrhosis, and 16 patients (6.3%) had none of the identified risk factors. Patients with ESRD but without risk factors had higher serum albumin levels ($P < 0.01$) and a lower frequency of hypoglycaemic episodes ($P = 0.01$) than those with the identified risk factors.

During the study period, 74 patients (28.9%) died, and 20 (7.8%) were transferred to other centres. The most common cause of death was infection (n = 36), followed by cardiac disease (n = 19), stroke (n = 4), malignancy (n = 2), respiratory disease (n = 2), gastrointestinal bleeding (n = 2) and unknown cause (n = 9). The distribution of patients and total mortality according to the lowest serum glucose level are shown in Figure 1. The degree of hypoglycaemia did not correlate with total mortality rate ($P = 0.08$). No significant association was noted between the number of hypoglycaemic episodes and total mortality (1 episode, 26%; 2 episodes, 41%; >2 episodes, 29%; $P = 0.11$). Logistic regression analysis for total mortality indicated that age (OR, 1.06; 95% CI, 1.03–1.10; $P < 0.001$), low serum albumin level (OR, 0.42; 95% CI, 0.24–0.74; $P = 0.003$) and infections (OR, 2.42; 95% CI, 1.17–5.01; $P = 0.02$) were independent risk factors (Table 3).

The occurrence of hypoglycaemia in patients receiving dialysis appeared to be a life-threatening complication as 27.0% of deaths (n = 20) occurred within 48 h of a hypoglycaemic episode. The distribution of patients with

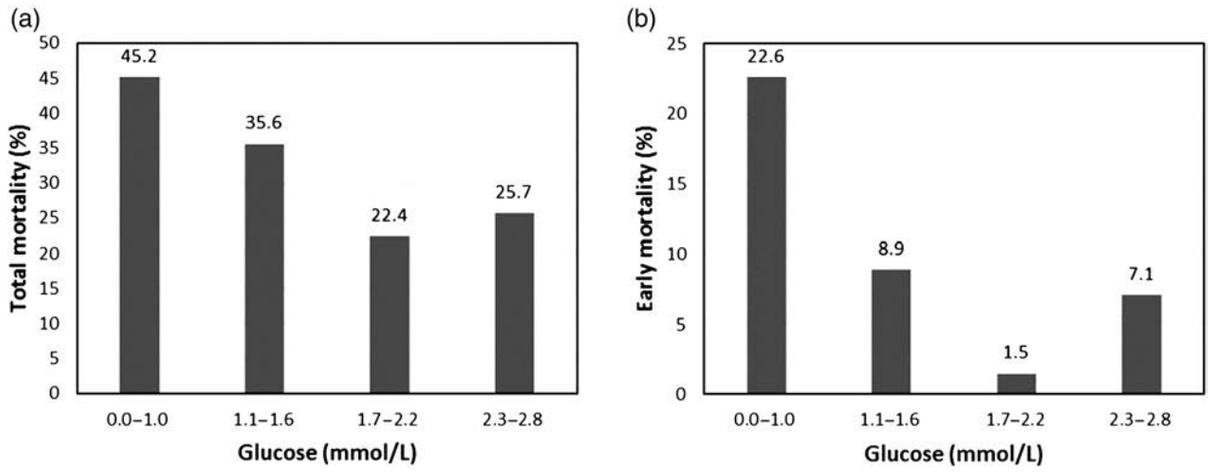

Figure 1 Total (a) and early (b) mortality according to glucose level in dialysis patients with hypoglycaemia (P = 0.08, 0.004).

early mortality according to the lowest serum glucose level is shown in Figure 1. Lower glucose levels were significantly associated with early mortality. There was no significant association between the number of hypoglycaemic episodes and early mortality (1 episode, 9%; 2 episodes, 4%; >2 episodes, 5%; P = 0.44). Logistic regression analyses for early mortality showed that the absence of diabetes (OR, 9.24; 95% CI, 2.64–32.35; P = 0.001), being older (OR, 1.09; 95% CI, 1.03–1.16; P = 0.003) and low serum glucose levels (OR, 0.95; 95% CI, 0.91–0.99; P = 0.02) were independent risk factors (Table 4).

Table 3 Independent factors associated with mortality in hypoglycaemic patients

Variables	Odds ratio (95% confidence interval)	*P*
Unadjusted		
Age (year)	1.06 (1.04–1.09)	<0.001
Male gender	0.83 (0.49–1.40)	0.48
Albumin (g/L)	0.33 (0.22–0.51)	<0.001
History of cardiovascular disease	1.36 (0.81–2.29)	0.25
Infection	4.03 (2.25–7.23)	<0.001
Malnutrition	1.58 (0.79–3.14)	0.20
Glucose (mmol/L)	0.97 (0.95–0.99)	0.01
Diabetes mellitus	0.96 (0.53–1.73)	0.88
Phosphorus (mmol/L)	0.88 (0.79–0.97)	0.02
Creatinine (μmol/L)	0.86 (0.78–0.95)	0.01
Duration of dialysis >24 months	0.75 (0.44–1.28)	0.29
Adjusted		
Age (year)	1.05 (1.02–1.08)	0.001
Albumin (g/L)	0.48 (0.28–0.83)	0.008
Infection	2.91 (1.42–5.96)	0.004
History of cardiovascular disease	1.70 (0.89–3.22)	0.11
Glucose (mmol/L)	0.98 (0.95–1.01)	0.15
Phosphorus (mmol/L)	0.99 (0.87–1.12)	0.89
Creatinine (μmol/L)	0.99 (0.89–1.11)	0.91

Discussion

Hypoglycaemia has been known to be a common problem in patients receiving dialysis since Block and Rubenstein reported it for the first time in 1970.[12] Hypoglycaemia is

Table 4 Independent factors associated with early mortality in hypoglycaemic patients

Variables	Odds ratio (95% confidence interval)	*P*
Unadjusted		
Age (year)	1.07 (1.02)	0.004
Male gender	1.16 (0.46)	0.75
Albumin (g/L)	0.57 (0.29)	0.11
History of cardiovascular disease	0.80 (0.32)	0.65
Infection	3.07 (1.22)	0.018
Malnutrition	0.95 (0.27)	0.94
Glucose (mmol/L)	0.95 (0.92)	0.009
Non-DM	4.94 (1.92)	0.001
Phosphorus (mmol/L)	0.95 (0.78)	0.59
Creatinine (μmol/L)	0.90 (0.77)	0.22
Duration of dialysis >24 months	3.01 (1.01)	0.04
Adjusted		
Age (year)	1.09 (1.03–1.16)	0.003
Albumin (g/L)	0.69 (0.28)	0.42
Infection	1.66 (0.46)	0.44
Glucose (mmol/L)	0.95 (0.91)	0.02
Non-DM	9.24 (2.64)	0.001
Duration of dialysis >24 months	2.35 (0.58–9.50)	0.23

DM, diabetes mellitus.

often multifactorial, even in patients with diabetes. Fisher *et al*. reported that in the majority of cases, hypoglycaemia is associated with renal insufficiency, liver diseases, infections, shock, pregnancy, neoplasms or burns[13] Chronic renal failure was noted in 25–49% of patients with hypoglycaemia.[13,14]

The incidence of 15.2% determined in our study was significantly higher than those reported in previous studies conducted on hypoglycaemia in hospitalised patients with ESRD. Haviv *et al*. reported that 56 patients (3.6%) had documented hypoglycaemia among 1545 hospitalised patients with ESRD. In that study, 34 patients were under haemodialysis, six under peritoneal dialysis and 16 (28.6%) did not receive dialysis.[1] In our study, all patients received haemodialysis or peritoneal dialysis. Therefore, the incidence of hypoglycaemia might have been higher than in previous studies. We found that hypoglycaemia was more common in patients with diabetes than in those without it. We noted a trend towards a higher incidence of hypoglycaemia in patients receiving haemodialysis than in those receiving peritoneal dialysis; however, the difference in incidence was not statistically significant. The relatively lower incidence of hypoglycaemia in patients receiving peritoneal dialysis could be associated with the use of glucose-containing dialysates in these patients.

The causes of hypoglycaemia in patients with renal failure include decreased caloric intake, reduced renal gluconeogenesis caused by a reduction in functioning renal mass, impaired release of counterregulatory hormones arising from the autonomic neuropathy of renal failure,[15] concurrent hepatic disease and decreased metabolism of drugs.[16,17] Under normal conditions, hepatic and renal glucose production rates are 11% and 89% respectively. Renal gluconeogenesis is known to increase in cases of diabetes mellitus and may be responsible for 30% of the total body production of glucose in dogs.[16] Thus, the role of renal glucose production is more substantial in patients with diabetes, and reduced renal gluconeogenesis caused by a reduction in the functioning renal mass may lead to hypoglycaemia in those with ESRD. Although the incidence rate of hypoglycaemia was high in this study, hypoglycaemia was not associated with mortality, whereas serious illness was.

Several factors may lead to the development of hypoglycaemia in patients receiving dialysis. Drug-induced hypoglycaemia is an important cause. Insulin, oral hypoglycaemic agents and several other drugs are not effectively eliminated in patients with ESRD.[18] In a study of hospitalised patients, insulin-related hypoglycaemia was found to be responsible for 95% of the episodes in those with diabetic nephropathy[13] Our results showed that insulin therapy (74.1% of patients with diabetes) was the most common risk factor for hypoglycaemia in patients receiving dialysis. Chronic malnutrition and infections are also often present in patients with ESRD and can contribute to the development of hypoglycaemia.[19] Malnutrition was a common risk factor in 15.6% of the cases of hypoglycaemia among our study patients. Furthermore, 26.6% of all the patients with hypoglycaemia had infection. Proinflammatory cytokines have been reported to cause enhanced systemic consumption of glucose, depletion of glycogen from the liver and muscle and impaired hepatic gluconeogenesis.[20] In particular, infections and malnutrition were found to be associated with poor outcomes in such patients. Similarly, Haviv *et al*. documented that the mortality rate caused by sepsis in hypoglycaemic patients was 66%, whereas in malnourished patients, it was 17%.[1]

Multivariate analysis showed that low serum albumin levels, infections and advanced age were independent risk factors associated with total mortality. A previous study of hospitalised elderly patients also indicated that sepsis, low albumin level and malignancy were independent predictors of mortality, whereas hypoglycaemia was not.[21] We infer that early mortality was related to hypoglycaemia because we believe that the effect of hypoglycaemia does not last long. In the present study, the occurrence of hypoglycaemia in patients receiving dialysis was associated with early mortality because 27.0% of patients died within two days of the onset of an episode. The degree of hypoglycaemia was also correlated with early mortality, indicating that severe hypoglycaemia is an important risk factor for death in patients receiving dialysis. The absence of diabetes, old age and low serum glucose level were found to be closely associated with early mortality.

This study had several limitations. First, it was a retrospective study based on the records of patients with documented blood glucose levels. Therefore, we do not have data on whether they had symptoms of hypoglycaemia at the time of sampling. Second, the prevalence of hypoglycaemia in this study might have been overestimated because glucose could have entered the samples during the transit to the laboratory if the samples were not assayed promptly. Third, hypoglycaemic episodes occurring at home were not accounted for, and we did not investigate whether the hypoglycaemic episodes occurred with the dialysis treatments or not. Fourth, we were unable to obtain any data about the association of hypoglycaemia with autonomic or peripheral neuropathy. Fifth, we did not investigate peritoneal dialysate glucose concentration.

Conclusion

We found that hypoglycaemia developed in patients receiving dialysis at a relatively high incidence. Multivariate analysis showed that older age, low serum albumin levels and infections were independent risk factors associated with total mortality, whereas hypoglycaemia was not. With respect to early mortality, the absence of diabetes, older age and low serum glucose levels were independent factors. Therefore, we recommend that elderly hypoglycaemic patients, especially those without diabetes mellitus, should be monitored closely.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1 General characteristics of hypoglycemic patients between hemodialysis and peritoneal dialysis.

Off-label use of tumour necrosis factor-alpha inhibitors and anakinra at an Australian tertiary hospital

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Key words
off-label use, TNF-alpha inhibitor, IL-1 inhibitor, clinical audit.

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Abstract

Background: Tumour necrosis factor-alpha inhibitors (anti-TNFα) and anakinra are monoclonal antibodies against pro-inflammatory cytokines overexpressed in many systemic inflammatory diseases. In Australia, they are registered for the treatment of several rheumatological, gastroenterological and dermatological indications. Despite increasing observational evidence for their use in off-label indications, there is a paucity of outcome research from the Australian hospital sector.

Aims: To describe the off-label use of anti-TNFα and anakinra at a tertiary referral hospital in Queensland, Australia and consideration of a drug register to inform future clinical decision-making.

Methods: We performed an in-depth retrospective chart audit of off-label treatment with anti-TNFα or anakinra at the Royal Brisbane and Women's Hospital from mid-2010 to mid-2014, linking demographic, phenotypic, pathology and outcome data with these drugs.

Results: Off-label use was identified in 10 patients. The most frequent indications were sarcoidosis and dermatological conditions. Three patients required sequential therapy with a second anti-TNFα (total responses = 13). Complete response occurred in 46%, partial response in 38% and primary non-response in 8%. Response was unable to be determined in 8%. We recorded 14 adverse events (infections most common).

Conclusion: This study suggests that anti-TNFα may be beneficial for some off-label indications (e.g. sarcoidosis). However, the observational design of this study (and pre-existing research) limits the ability to infer causality and generalise results. We propose the creation of a mandatory drug register to monitor off-label use. Whilst comparative efficacy cannot be established without a matched placebo arm, a register would enable some reporting on effectiveness in rare diseases and identify infrequent but serious adverse events.

Introduction

Tumour necrosis factor-alpha inhibitors (anti-TNFα) including infliximab, etanercept, adalimumab and the interleukin-1 receptor antagonist anakinra are high molecular weight proteins (biologics) that selectively target pro-inflammatory cytokines overexpressed in many chronic inflammatory and autoimmune diseases.[1,2] Approved indications now extend beyond the initial Food and Drug Administration licensed conditions of Crohn disease (CD) (infliximab in mid-1998) and rheumatoid arthritis (RA) (etanercept late 1998) to other systemic inflammatory diseases.

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In Australia, the Therapeutic Goods Administration (TGA)-registered and Pharmaceutical Benefits Scheme (PBS)-subsidised use of anti-TNFα requires the failure of conventional first-line therapy before use in dermatological (plaque psoriasis), rheumatological (ankylosing spondylitis, juvenile idiopathic arthritis, psoriatic arthritis, RA) and gastroenterological (CD, ulcerative colitis) indications. Government subsidy allows patients to access these high cost medications (i.e. >AUD $10 000 per annum), which are significantly more expensive than first-line therapies. While anakinra is registered for the treatment of RA and cryopyrin-associated periodic syndromes, it is no longer subsidised by the Pharmaceutical Benefits Scheme for the treatment of RA (poor cost-effectiveness).

There is increasing evidence for off-label use of anti-TNFα in the treatment of systemic inflammatory

disorders including sarcoidosis, Behçet disease and non-infectious uveitis.[3,4] 'Off-label' usually refers to the prescribing of a medication for an indication, route of administration or patient population that is not registered by the TGA (in Australia). Off-label prescribing can be important in areas of clinical practice where treatment options are limited or research is challenging (e.g. paediatrics).[5] While off-label use is legal, it is a prescriber's responsibility to defend their prescribing with reasonable quality evidence.[6] Plausibility for the off-label effectiveness of anti-TNFα and anakinra has mainly been inferred from observational research, often without placebo comparisons due to low prevalence rates in the general population.[4] High quality evidence is therefore not available to support routine use and cyclical revision of practice protocols.

Off-label use of anti-TNFα or anakinra at our institution, the Royal Brisbane and Women's Hospital (RBWH), requires approval by the High Cost Drug Committee (HCDC). This committee investigates the efficacy, safety and cost-effectiveness of an off-label medication in comparison to standard therapy for the treatment of a particular patient. HCDC approval is a common method of funding expensive drugs with little or no evidence for low prevalence indications, such as many of the inflammatory diseases.

We aimed to identify and describe off-label treatment with anti-TNFα and anakinra at the RBWH, a large university teaching and tertiary referral hospital in Brisbane, Australia. These data may help guide payers when making decisions about off-label use of expensive medications, with the potential for cost savings and improved access to effective treatments.

Methods

This retrospective and descriptive audit was undertaken at the RBWH. Off-label was defined as use for an indication without TGA approval. Patients who received an anti-TNFα (infliximab, adalimumab or etanercept) or anakinra for an off-label indication between August 2010 and September 2014 were identified through HCDC meeting minutes. We could not access HCDC minutes before August 2010, so this study is limited to a 4-year period. Exemption from full ethical review was approved through the chairperson of the RBWH Human Research Ethics Committee. Ref No.: HREC/14/QRBW/349.

The audit used patient medical records (paper and electronic charts) to collect demographic data (age, sex), previous treatment, indication, anti-TNFα/anakinra used, doses given, outcome and adverse event data. This methodology follows similar chart audits of the off-label use of rituximab (monoclonal antibody against CD20 on B lymphocytes) at large tertiary hospitals.[7,8]

Data are analysed in a descriptive manner. Adverse events are detailed using the Medical Dictionary for Regulatory Activities terms. Outcomes were recorded using objective clinical data where possible. However, this was difficult to attain for many indications due to the nature of the medical condition and/or inadequate documentation including specifics on outcomes. In these indications, the response is presented subjectively using free text as described by the clinicians in patient records. Disease activity scores were not included as they are not routinely documented in patient records and are difficult to calculate retrospectively.

Outcome criteria for eight indications were used to determine a response type (Table 1). Importantly, response type was described in terms of response to an individual agent as several patients received more than one anti-TNFα over the period. Outcome criteria include both objective outcomes and the subjective appreciation of response as described by the clinician and/or patient in the patient record. Data from patient records before, during and after biological treatment were analysed with outcome criteria to establish response type.

Response types are similar to those used previously[9] and consist of:

1 Complete response (CR): objective and/or subjective improvement without disease flares on treatment.
2 Partial response (PR): divided into three subcategories including secondary non-response (loss of response after initial period of clinical benefit), clinical benefit with disease flares and intolerance on re-initiation.
3 Primary non-response: no objective and/or subjective improvement during induction therapy.
4 Unable to determine response: not enough data available.

Results

We identified 10 patients who received etanercept, adalimumab, infliximab or anakinra for an off-label indication at the RBWH between August 2010 and September 2014. The time taken to audit each patient record was approximately 5 h.

Individual patient data have been summarised in a case-based format (Supporting information, Appendix S1). Patients were prescribed an average of four conventional, first-line medications prior to treatment with an anti-TNFα or anakinra. Two anti-TNFα agents were trialled sequentially by three patients. Reasons for change in therapy included secondary non-response (one case),

Table 1 Outcome criteria used to determine response type across selected indications

Indication	Outcome criteria
Pyoderma gangrenosum	– Clinical improvement in skin lesion severity and size – Photographic monitoring
Metastatic cutaneous CD	– Clinical improvement in skin lesion severity and size – Photographic monitoring
Schnitzler syndrome	– Clinical improvement including dermatological (urticarial rash) and systemic symptoms (arthralgia, myalgia, bone pain, lymphadenopathy and intermittent fevers) – Inflammatory markers (CRP)
TRAPS	– Clinical response including decreased frequency and severity of fevers, myalgia, conjunctivitis, periorbital oedema, abdominal pain, monoarticular arthritis, rash – Inflammatory markers (CRP, ESR)
Sarcoidosis (including pulmonary sarcoidosis, sarcoidosis with ophthalmic involvement and neurosarcoidosis)	– Symptomatic improvement in disease activity including improved exercise tolerance, decreased dyspnoea – Inflammatory markers (CRP, ESR) – Serum Ca^{2+} – Serum ACE level – Pulmonary imaging (CXR, HRCT) – Pulmonary function testing (FEV1, FVC, DLCO) – Neurosarcoidosis (MRI and physical examination) – Ophthalmic involvement (ophthalmic examination including VA)
Retinal vasculitis	– Symptomatic improvement – Ophthalmic examination including VA
Behçet disease with uveitis	– Symptomatic improvement including improvements in mucocutaneous ulcers and ocular disease – Ophthalmic examination including VA

ACE, angiotensin converting enzyme; Ca^{2+}, calcium; CD, Crohn disease; CRP, C-reactive protein; CXR, chest radiograph; DLCO, diffusing capacity of the lung for carbon monoxide; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution computed tomography; MRI, magnetic resonance imaging; TRAPS, tumour necrosis factor receptor-associated periodic syndrome; VA, visual acuity.

unable to tolerate re-initiation (one case) and no reason given or identified (one case). Consequently, response to therapy has been documented per biologic agent (total number of responses is 13).

CR was seen in six cases (46%), PR in five cases (38%) and primary non-response in one case (8%) (Table 2). In one case (8%), response was unable to be determined primarily due to inadequate patient documentation and missing information. PR was divided into three categories for more detailed analysis – three cases (60%) of clinical benefit with disease flares on anti-TNFα, one case (20%) of secondary non-response and one case (20%) of intolerance on re-initiation of anti-TNFα.

Sarcoidosis and dermatological conditions (pyoderma gangrenosum, cutaneous CD) were the most frequent indications (Table 2). Schnitzler syndrome was the only condition that had no response to treatment.

A total of 14 adverse events was identified using Medical Dictionary for Regulatory Activities terms (Table 3) – it was difficult to determine whether one adverse event was treatment emergent due to inadequate documentation. The most common adverse events were infections (five cases), administration site reactions (three cases) and generalised rash (three cases). Four patients experienced two or more adverse events while on biologic therapy. Most patients were on concomitant immune suppression throughout treatment with anti-TNFα or anakinra.

Discussion

Randomised clinical trial data for each new biologic agent in each disease are often unavailable due to the small numbers of patients with these types of diseases. However, clinician experience suggests anti-TNFα or anakinra can be helpful when used in the appropriate patient group. To our knowledge, this patient record audit is the first study investigating health outcomes with off-label use of anti-TNFα or anakinra in the Australian hospital sector. Partial or complete response was demonstrated in all off-label indications other than Schnitzler syndrome. The risk of treatment emergent adverse events was substantial. These results are likely to be clinically important, as all patients discussed at the HCDC had exhausted conventional therapy options.

Sarcoidosis was the most common indication identified. One in 10 patients with chronic sarcoidosis will have disease refractory to at least one conventional immunosuppressant agent.[10] Our study showed functional improvement with anti-TNFα in some patients with disease resistant to conventional therapy. This is consistent with a small randomised controlled trial of infliximab for refractory pulmonary sarcoidosis, which showed a small, yet, statistically significant improvement (2.5%) in forced vital capacity.[11] Observational studies document beneficial outcomes in sarcoid uveitis treated with adalimumab or infliximab and neurosarcoidosis treated with infliximab.[12,13] Interestingly, there is a paradoxical effect documented in case reports whereby anti-TNFα (adalimumab, etanercept, infliximab) induced

Table 2 Response type based on indication

Indication	Complete response	Partial response	Primary non-response	Unable to be determined	Number of cases
Sarcoidosis – pulmonary	1				1
Sarcoidosis – neurosarcoidosis		1		1	2
Sarcoidosis – panuveitis	1	1			2
Pyoderma gangrenosum	1				1
Metastatic cutaneous CD	1				2
Schnitzler syndrome			1		1
TRAPS		1			1
Behçet disease with uveitis	1	1			2
Bilateral retinal vasculitis	1				1
Total	6 (46%)	5 (38%)	1 (8%)	1 (8%)	13

CD, Crohn disease; TRAPS, tumour necrosis factor receptor-associated periodic syndrome.

Table 3 Adverse events – number and type using MedDRA terms

Adverse events	*n*
General disorders and administration site conditions:	
Administration site reaction	3
Skin and subcutaneous tissue disorders:	
Drug eruption	1
Rash generalised	3
Gastrointestinal disorders:	
Abdominal pain	1
Neurological disorders:	
Dizziness	1
Infections and infestations:	
Tinea versicolor	1
Upper respiratory tract infections	1
Lower respiratory tract and lung infections	1
Skin and subcutaneous tissue infections and infestations:	
Furuncle or carbuncle	1
Skin infection and subcutaneous tissue infections (NEC)	1
Total	14

MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified.

sarcoidosis in patients treated for other autoimmune indications.[14–16]

All other indications except Schnitzler syndrome (treated with anakinra) demonstrated partial or CR to treatment. Although we saw a PR with etanercept for the treatment of tumour necrosis factor receptor-associated periodic syndrome, previous research has shown variable efficacy and high discontinuation rates.[17] Use in the other identified off-label conditions is guided by favourable results from uncontrolled research with small sample sizes, similar to this study.[18–24]

Three patients in our study were treated sequentially with two off-label anti-TNFα agents. Reasons for changing agents included secondary non-response and intolerance on re-initiation. Previous research suggests loss of response may be due to inadequate drug concentrations (from anti-drug antibodies, non-adherence or non-immune clearance) or inflammation not responsive to TNF-α inhibition.[25] Secondary non-response is reported in up to 50% of RA patients treated with infliximab in the first year.[26] The seemingly paradoxical immunogenicity of anti-TNFα may also explain higher rates of intolerance with re-initiation and increased drug survival with concomitant immune suppression.[27] Optimising treatment efficacy by monitoring anti-TNFα concentrations has been suggested and is currently under consideration by the Gastroenterological Society of Australia (R. Leong, pers. comm., 2016).

In our audit, the most common adverse reactions were administration site reactions and infection. We also saw a case of tinea versicolor, previously reported.[28] The observational design made it difficult to compare rates of adverse events in our study with previous research. Further, most large trials of an anti-TNFα or anakinra reported rates of serious bacterial infections only.

Our study has some limitations. Data were obtained retrospectively from individual indications with small sample sizes. The accuracy of recorded data was impeded by inadequate documentation by clinicians (e.g. in one neurosarcoidosis case, the lack of documentation of physical examination findings made interpretation of an outcome impossible) and the subjective, non-standardised nature of data documented. Furthermore, in many institutions, including ours, different clinicians treat patients throughout their illness. This increases the likelihood of inter-observer variation with the documentation of non-standardised data.

Throughout the audit subjective assessment of written information within patient records was required to determine response in many indications, creating the potential for personal biases to influence the interpretation of results. While only a single reviewer (ML) performed the chart audit, the risk of subjective interpretation was negated through the use of pre-defined outcome criteria.

Despite the limitations posed by this study and other observational research, an observational design is often the only approach for low prevalence conditions. Off-label therapies may become the accepted standard of care in conditions where 'gold standard' research is lacking and limited treatment options exist.[29,30] Failure to examine a new therapy prior to widespread use in clinical practice creates potential problems. These include the inability to determine the ideal dose, length of treatment or patient population, and the opportunity cost of impeding access to more effective therapy.

As many of these conditions have a low prevalence in the community, a mechanism is needed to synthesise evidence from multiple locations so that the efficacy and safety of high cost medicines can be better investigated. Without such a mechanism, the current system of registration and subsidisation biases diseases that occur with higher frequency. Other authors have made similar proposals, suggesting the need for improved research design and more integrated and accessible data systems, such as nationwide registers, that can better encompass populations typically excluded from 'gold standard' research.[31,32] Registers are an underused resource in Australian clinical research that would inform clinical and policy decision-making with potential savings for healthcare systems.[31]

We propose a nationwide mandatory drug register to monitor the off-label use of anti-TNFα and anakinra, with the potential to expand to other high cost medications. Whilst this is important now, it will become increasingly important with the marketing of biosimilars, which will have even less clinical trial data for registration than the originator biologics. Collecting information at a national level will provide data for low prevalence indications.

Conclusion

Anti-TNFα and anakinra are expensive medications increasingly used in several off-label indications, usually in the absence of any good evidence. We found that anti-TNFα were potentially effective in some off-label indications albeit with risk of adverse events. Part of the reason why these agents remain off-label is that the current system of registration and subsidisation biases those indications amenable to 'gold standard' research design. The formation of a national mandatory drug register to monitor the off-label use of anti-TNFα and anakinra could guide payers when making decisions around the treatment of rare diseases with these expensive medicines.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix S1 Patients receiving off-label etanercept, adalimumab, infliximab and anakinra.

Outcomes of patients with non-melanoma solid tumours receiving self-funded pembrolizumab at Chris O'Brien Lifehouse

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Key words
pembrolizumab, immunotherapy, end-of-life, advanced cancer, futility.

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Abstract

Background: Immunotherapy agents show anti-cancer activity in several solid cancers. Efficacy in non-melanoma solid tumours for non-approved indications is unknown.
Aim: To evaluate patient and disease characteristics, rate and duration of response, and toxicity of self-funded pembrolizumab in patients with non-melanoma solid cancers.
Method: Retrospective review describing outcomes and toxicity of self-funded pembrolizumab in patients with non-melanoma solid cancers treated at Chris O'Brien Lifehouse.
Results: From April 2015 to December 2015, 21 patients received or were planned to receive self-funded pembrolizumab. The median age was 50 years (16–76), 28 and 10% had an Eastern Cooperative Oncology Group performance status of 2, and 3–4 respectively. Sixty-two percent received at least two to four lines of prior drug treatment. Median follow-up was 3.0 months (range, 0.4–9.6). Fourteen (67%) patients requested pembrolizumab. Pembrolizumab was clinician offered for 7 (33%) patients. Patients who requested pembrolizumab had worse outcomes. Three patients died before receiving pembrolizumab. Of the 18 patients that received at least one dose, a partial response was observed in 3 (17%). Progressive disease occurred in 83%. Four patients received only one cycle of pembrolizumab and died after a median of 27 days (range 13–43). Immune-related adverse events of any grade occurred in 33%. No grade 3–4 events were observed.
Conclusion: Pembrolizumab was well tolerated. Meaningful responses were observed in 17% of treated patients. Response continues after 5–6.5 months follow-up in 11% and >8 months of follow-up for the other responding patient. Financial impact to the patient can be substantial. Outcomes for 33% were poor with three patients dying prior to receiving therapy and four dying within weeks of receiving one dose. This highlights issues regarding the careful selection of patients, futility of anti-cancer therapy at the end-of-life and patients' perceived benefit of receiving this therapy.

Introduction

The advent of immune checkpoint blockade is considered a revolution by some in cancer therapy progress. Nivolumab and pembrolizumab are anti-PD-1 antibodies evaluated in randomised trials demonstrating improvements in survival in patients with metastatic melanoma, renal cell carcinoma and non-small cell lung cancer.[1–3] Therapy is generally well tolerated and responses can be durable.

In the era of rapid dissemination of information regarding advances in cancer care, desperate patients are increasingly seeking to access drugs on the basis of early data. They are ill equipped to critique or contextualise the evidence of benefit of these therapies. The desire to access such high cost therapy is exacerbated by the understandable enthusiasm of the medical, pharmaceutical and general community for these therapies in the media.

Encouraging efficacy signals with immune checkpoint inhibitors have been observed for a number of tumour types in early phase trials[4–8] leading to patients with solid tumours pursuing access to self-funded pembrolizumab. The outcome for patients receiving this treatment for non-approved indications is unknown.

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Conflict of interest: C. McNeil has served on advisory boards for MSD.

The aim of this retrospective study is to describe outcomes and associated toxicity of pembrolizumab in patients with non-melanoma solid organ malignancies treated at Chris O'Brien Lifehouse. These patients were not enrolled in clinical trials and consequently did not receive the drug under trial conditions.

Methods

Patients with non-melanoma solid organ malignancies who received or were planned to receive self-funded pembrolizumab were included. Pembrolizumab was administered intravenously at a dose of 2 mg per kg of body weight every 3 weeks. Immune-related adverse events (irAE) were graded according to the National Cancer Institute CTCAE, version 4.0.[9] Time to progression (TTP) was calculated from the date of pembrolizumab commencement until date of progression or death for patients that received at least one dose of pembrolizumab. Time to response (TTR) was calculated from the date of pembrolizumab commencement to the date of radiological response. Response was assessed as per RECIST 1.1.[10] Ethics committee approval was obtained for publication of this retrospective data (X15-0422; LH16.004).

Results

Between April and December 2015, 21 patients received or were planned to receive self-funded pembrolizumab. Patient and disease characteristics are described in Table 1. Malignancy type included six patients with a diagnosis of mesothelioma and nine patients with sarcoma. The remaining six patients had diagnoses of an undifferentiated carcinoma of the parotid, urothelial carcinoma, mucoepidermoid carcinoma, nasopharynx squamous cell cancer, non-small cell lung adenocarcinoma and an anal squamous cell cancer. The median age was 50; 57% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, 28% an ECOG of 2 and 10% had an ECOG of 3–4. Twenty-eight percent and 62% of patients had received 0–1 and at least two to four lines of prior treatment respectively. In 9% of patients, the number of prior treatment lines was unknown, but described as heavily pre-treated in the medical record. The median duration of follow-up was 3.0 months (range, 0.4–9.6). At the time of last follow-up, 11 patients had died.

The median number of pembrolizumab doses received was 3 (range 0–9), with two patients still receiving treatment at the time of last follow-up and one patient undergoing a treatment break after an excellent metabolic response on positron emission tomography (PET) scan.

Of the 21 patients, 14 (67%) requested pembrolizumab therapy and for 7 (33%) patients, this was offered by the clinician. Patients who requested pembrolizumab therapy had worse outcomes with a shorter TTP of 39 days (7–57) compared with 75 days (17–90) (Table 2).

Three patients died before receiving pembrolizumab. No patients achieved a complete response (CR) to pembrolizumab. Of the 18 patients that received at least one dose of pembrolizumab, a partial response (PR) was confirmed in 3 (17%). Fifteen of the 18 patients that received at least one dose of pembrolizumab (83%) had progressive disease (PD) (Table 3).

Table 1 Patient characteristics

Patient characteristics	Self-funded pembrolizumab, *n* = 21	Patient requested, *n* = 14/21 (67%)	Clinician offered, *n* = 7/21 (33%)
Median age (range) – year	50 (16–76)	61 (25–76)	43 (16–75)
Male sex – number (%)	17 (81%)	11 (52%)	6 (29%)
ECOG performance status – number (%)			
0–1	12 (57%)	9 (43%)	3 (14%)
2	6 (28%)	3 (14%)	3 (14%)
3–4	2 (10%)	1 (5%)	1 (5%)
Unknown	1 (5%)	1 (5%)	0
Pre-existing autoimmune condition	1 (5%)	1 (5%)	0
Malignancy type			
Mesothelioma†	6 (28%)	6 (28%)	0
Sarcoma††	9 (43%)	5 (24%)	4 (19%)
Other§	6 (28%)	3 (14%)	3 (14%)
Prior lines of treatment – number (%)			
0–1	6 (28%)	5 (24%)	1 (5%)
2–4	13 (62%)	8 (38%)	5 (24%)
Unknown 'heavily pre-treated'	2 (9%)	1 (5%)	1 (5%)

†Epithelioid, *n* = 5; sarcomatoid, *n* = 1. ††Osteosarcoma, *n* = 3; synovial sarcoma, *n* = 1; Ewing sarcoma, *n* = 3; leiomyosarcoma, *n* = 1, angiosarcoma, *n* = 1. §Undifferentiated parotid, *n* = 1; urothelial, *n* = 1; mucoepidermoid, *n* = 1; nasopharynx squamous cell, *n* = 1; NSCLC adenocarcinoma ca., *n* = 1; anal squamous cell, *n* = 1. ECOG, Eastern Cooperative Oncology Group.

Table 2 Pembrolizumab therapy: clinician offered versus patient requested

Self-funded pembrolizumab, *n* = 21 (%)			
	Requested by patient 14/21 (67%)	Offered by clinician 7/21 (33%)	Total
Died before receiving pembrolizumab	2 (9%)	1 (5%)	3 (14%)
PR	1 (5%)	2 (9%)	3 (14%)
PD	11 (52%)	4 (19%)	15 (71%)
Median TTP/death days (range)	39 (7–57)	75 (17–90)	39 (7–90)

PD, progressive disease; PR, partial response; TTP, time to progression.

Patients achieving partial response

Three (17%) of 18 patients treated with pembrolizumab had a PR.

Patient 1

A 65-year-old male with undifferentiated carcinoma of the parotid with lung metastases – This patient had an ECOG performance status of 2 at the time of commencing pembrolizumab and had received three prior lines of therapy. He had a reduction in tumour burden of −84% determined by RECIST 1.1 (Fig. 1). TTR was 1.7 months and is ongoing after 5.4 months of follow-up. This patient developed a dermatological irAE of grade 1 severity.

Patient 2

A 75-year-old male with a urothelial malignancy with lung, retroperitoneal and mesenteric metastases – This patient had not received any prior lines of therapy as chemotherapy was contraindicated due to pre-existing myelodysplasia. He had an ECOG of 0 when commenced on pembrolizumab. He had an excellent metabolic response on PET with TTR of 2 months and is maintained after 6.5 months of follow-up. This patient developed grade 1 dermatological and thyroid toxicity.

Treatment with pembrolizumab was ongoing for the above two patients at the date of last follow-up.

Table 3 Response to treatment

Tumour response	Received ≥1 dose pembrolizumab, *n* = 18
Best overall response at any assessment	
CR	0 (0%)
PR†	3 (17%)
SD	0 (0%)
PD††	15 (83%)

†RECIST 1.1, *n* = 1; PET metabolic response, *n* = 2. ††RECIST 1.1, *n* = 7; PET, *n* = 4; clinical, *n* = 4. CR, complete response; PD, progressive disease; PR, partial response; SD, symptomatic decline.

Patient 3

A 25-year-old male with a diagnosis of Ewing sarcoma with lung and bone metastases – This patient had received multiple prior lines of therapy although the precise number was not documented. He had an ECOG performance status of 0 at commencement of pembrolizumab and achieved a sustained metabolic response on PET.[11] TTR was 2 months and continues after 8.4 months of follow-up. He developed grade 2 hypothyroidism requiring thyroxine replacement as an irAE. Due to disease response and significant financial costs of self-funding therapy, the patient received nine cycles of pembrolizumab followed by observation with regular imaging to assess for disease progression.

Non-responders to pembrolizumab

Fifteen (83%) of the 18 patients that had received at least one dose of anti-PD-1 therapy experienced PD. Median TTP was 39 days (range 7–90). Of these 15 patients, five received subsequent lines of anti-cancer therapy. These five patients had a median age of 31 (range 16–62) and an ECOG performance status ranging from 0 to 4. All had received prior lines of treatment (range 1–3). One had a temporary improvement in performance status, three remained clinically stable and one had symptomatic decline while receiving pembrolizumab.

The nine patients that did not receive further lines of treatment had a median age of 62 (range 24–76) and ECOG performance status ranging from 0 to 2. They had received zero to four prior lines of therapy. Eight patients had symptomatic decline with four experiencing rapid decline. In one patient, clinical symptoms were not documented due to transfer of care overseas; however, this patient died less than 2 months after starting pembrolizumab.

In one patient, documentation of any subsequent treatment was not recorded.

Four patients received only one cycle of pembrolizumab (Table 4) and all experienced PD. These patients had received two to four prior lines of treatment. They had a baseline ECOG of 1–2 followed by rapid clinical decline. These four patients died a median of 27 days (range 13–43) after receiving a single dose of therapy.

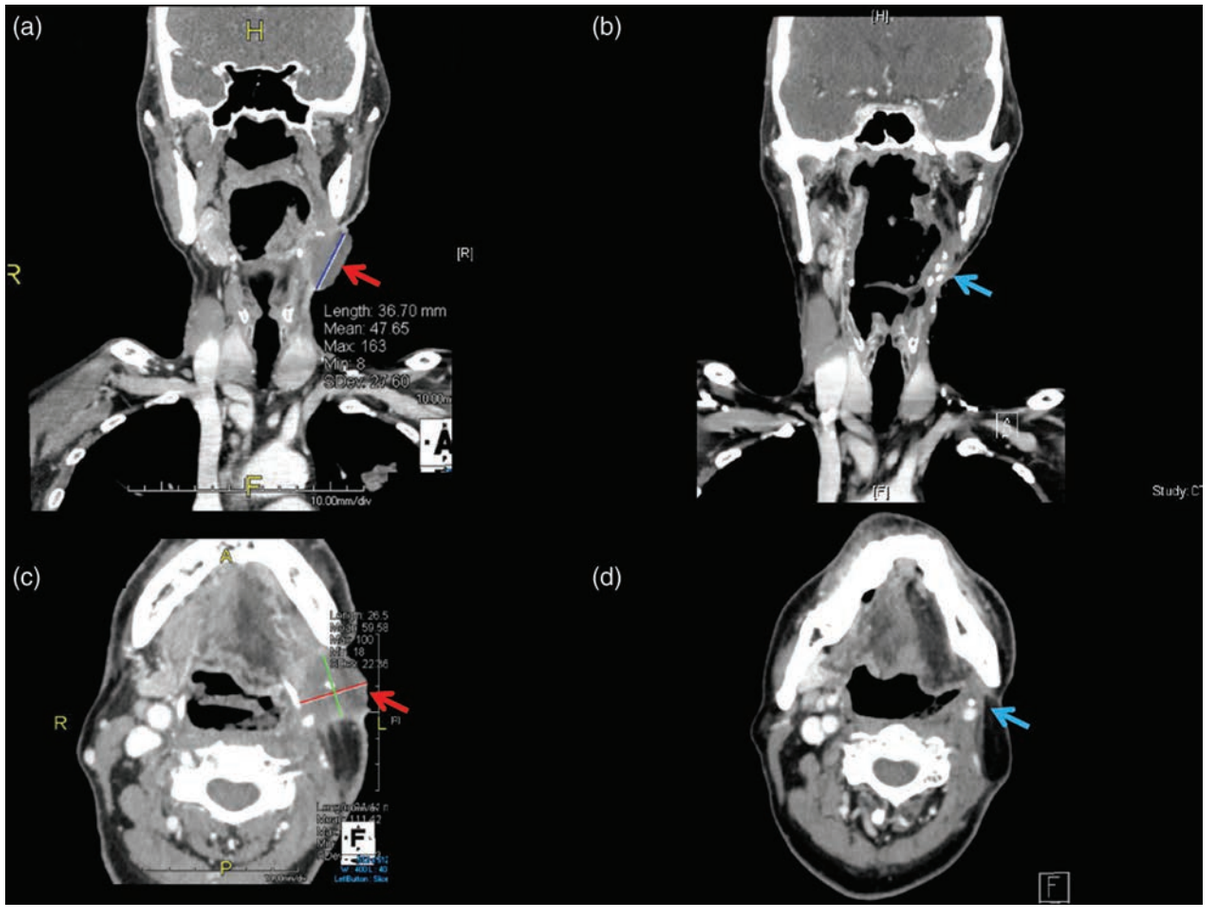

Figure 1 (a) Coronal view of exophytic tumour at the left angle of the mandible measuring 37 mm (red arrow), (b) poorly visualised after 4 months of pembrolizumab (blue arrow), (c) axial view of tumour, 27 mm × 25 mm (red arrow) and (d) difficult to appreciate after 4 months of pembrolizumab (blue arrow).

Death before receiving pembrolizumab

Three (14%) patients died prior to receiving pembrolizumab (Table 2).

Patient 1

A 61-year-old male with epithelioid pleural mesothelioma with diffuse peritoneal disease – He had received three prior lines of therapy. Pembrolizumab was requested by the patient. His ECOG performance status was one as per medical record documentation, but disease symptoms were rapidly increasing and cachexia was present at the time of seeking to self-fund pembrolizumab. Best supportive care had been offered as well as palliative chemotherapy with gemcitabine as alternatives to self-funded pembrolizumab.

Table 4 Pembrolizumab cycles received

Planned to receive pembrolizumab, *n* = 21	Outcome
Median number pembrolizumab cycles (range)	3 (0–9)†
Received one dose pembrolizumab only	4 (19%)
Median time from receiving first dose to death, days (range)	27 (13–43)
Died before receiving first dose pembrolizumab	3 (14%)

†*n* = 2 treatment is ongoing; *n* = 1 treatment break due to excellent response and financial cost.

Patient 2

A 47-year-old male with Ewing sarcoma with an ECOG of 2 at the time of discussing self-funded pembrolizumab – He had received three prior lines of therapy. Pembrolizumab was offered by the clinician. Within 4 weeks before his death, he was admitted with a symptomatic haemorrhagic brain metastasis causing focal neurology right-sided weakness and seizures. He proceeded to craniotomy and

resection followed by eventual decline in performance status and death.

Patient 3

A 50-year-old man with a mucoepidermoid carcinoma and a past history of glomerulonephritis – The patient had an ECOG of 1 documented within 3 weeks before his death and had received two prior lines of therapy. Pembrolizumab was requested by the patient. He experienced rapid progression of hepatic and brain disease. Liver derangement occurred with GT elevated at 19 times the upper limit of normal and AST 17 times the upper limit of normal equating to grade 3 severity. Possibly inefficacy of pembrolizumab had been discussed as well as not administering any further systemic therapy due to decline in clinical status.

Adverse events

Immune-related adverse events of any grade occurred in 6 (33%) patients (Table 5). Toxicities reported were mild, including four patients with skin toxicity, two patients with thyroid irAE and one patient experiencing joint and muscle toxicity. One patient with thyroid toxicity demonstrated a hyperthyroid phase followed by hypothyroid phase and the other required thyroxine replacement for grade 2 hypothyroidism. There were no grade 3–4 irAE.

Discussion

This retrospective review identified 21 patients with non-melanoma cancers that received or were planned to receive self-funded pembrolizumab at Chris O'Brien Lifehouse. Over two-thirds of patients in our cohort were heavily pre-treated, having received at least two to four prior lines of therapy, and 38% had an ECOG of 2–4. There are few data regarding the use of pembrolizumab in patients with these poor prognostic characteristics. Initial data from KEYNOTE-001 assessed pembrolizumab in multiple solid cancers (including melanoma) with 50% of patients having received three or more prior therapies.[5] However, no patients had an ECOG of 2–4 with 33 and 67% of patients having an ECOG of 0 and 1 respectively. In these initial 30 patients, 2 (7%) patients achieved a CR, 3 (10%) achieved a PR and 15 (50%) experienced symptomatic decline.

Table 5 Immune-related adverse events

irAE (received ≥1 dose pembrolizumab, n = 18)	Any grade (%)	Grade 3–4
Any	6 (33%)	0
Skin	4 (22%)	0
Thyroid†	2 (11%)	0
Joint and muscle	1 (6%)	0

†n = 1 thyroiditis (hyperthyroid followed by hypothyroid phase); n = 1 hypothyroid. irAE, immune-related adverse events.

In our cohort, 3 (17%) of patients who received at least one dose of pembrolizumab achieved meaningful responses. The responses were both radiologically and clinically significant and further demonstrate immunotherapy efficacy in multiple solid cancer types. Interestingly, an excellent metabolic response was seen in a patient with Ewing sarcoma. In early data from SARC028, PR rates to pembrolizumab were 19% for soft tissue sarcomas and 5% for bone sarcomas with no PR seen for Ewing sarcoma.[8] No responses were seen in any patient with non-small cell lung cancer or mesothelioma in this cohort. No patient experienced grade 3–4 immune-related toxicity and may reflect the short duration that pembrolizumab was prescribed.

Out of the 21 patients that sought to self-fund pembrolizumab, 3 (14%) patients died before the approved drug could be supplied and 4 (19%) died within 13–43 days of receiving a single dose of pembrolizumab. This outcome highlights several issues regarding the careful selection of patients, futility of anti-cancer therapy at the end-of-life and patients' perceived benefit of receiving this therapy.

Indicators of overly aggressive end-of-life cancer care have been identified with respect to chemotherapy use, but are lacking for immunotherapy agents. This includes, but is not limited to, receiving chemotherapy in the last 2 weeks of life, commencing a new line of chemotherapy in the last 30 days of life, the timing and delivery of hospice care.[12] Cancer treatment in patients nearing death has been reported to be increasingly aggressive in an analysis of more than 28 000 patients monitored by the SEER registry.[13] The use of chemotherapy within the last 4 weeks of life has been documented at rates of 12–18%[14,15] and 8% within the last 2 weeks of life.[15] The reasons for this are multifactorial and may include duration of palliative care involvement, gender[14] and individual clinician.[15] With data for immunotherapy showing promise in solid organ malignancies,[1–3] being better tolerated than cytotoxic agents with the possibility of durable responses, patients may feel compelled to pursue such therapy. In turn, this may delay appropriate transition to palliative care.

Despite documentation of best supportive care as an option to some of the patients in this cohort, patients persisted with seeking self-funded immunotherapy. We were not able to explore the level of understanding that patients had regarding their prognosis, perceived benefit of seeking self-funded therapy or possible futility. Nor were we able to document the level to which withdrawal

of anti-cancer therapy was discussed. Medical futility and the complex circumstances surrounding communicating this to patients has been described.[16] It involves undertaking a clinical action when it is clear that this action will not achieve the proposed goal and is doomed to fail.

The discrepancy between patients and physicians estimates of survival has been documented.[17] In a prospective study of 917 patients with advanced non-small cell lung or colon cancer, it was observed that patients overestimated their chance of surviving 6 months. Additionally, patients who believed they would survive for at least 6 months were more inclined to opt for life prolonging therapies rather than best supportive care. It is unknown if this influenced a proportion of the patients in our cohort, but would seem plausible. It may also be simpler for physicians to offer another line of therapy than it is to have a difficult discussion around withdrawal of treatment.[15,18]

Economic harm from massive out-of-pocket costs is a distinct issue for patients desperate to fund non-approved therapies.[19] Kantarjian *et al.* describes the crossing of a moral line between profiteering and the need for a fair price being applied to cancer drugs whereby it is affordable to those in need while reasonable profits are attained by the supplier.[20] During the period that this cohort of patients self-funded their therapy through a cost-share programme, the cost per 50 mg vial of pembrolizumab was $2230. For the average 70 kg patient, this equates to $6700 per cycle or $20 000 for three cycles. Patients were required to finance three of the first six cycles of treatment and all cycles of treatment thereafter were charged. The current cost-share programme charges $1472 per 50 mg vial with no free cycles. The degrees of financial burden by grades 1–5 (mild to castastrophic) have been described as a tool to identify patients at financial risk.[19] Financial burden was not assessed in this cohort and although a difficult issue to raise when discussing a terminal illness, it has influenced treatment decisions with one patient achieving a PR temporarily ceasing therapy as a consequence.

Conclusion

There are, of course, limitations of this data with our review being retrospective and descriptive with small patient numbers. Nevertheless, the information gleaned from this cohort demonstrates occasional activity of anti-PD-1 therapy in non-approved solid cancers with a low toxicity profile and sheds light on the shortcomings and difficulties in the management of cancer patients at the end-of-life.

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Patient characteristics, interventions and outcomes of 1151 rapid response team activations in a tertiary hospital: a prospective study

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rapid response teams, tertiary hospital, prospective study, patient characteristics, interventions, outcomes.

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Abstract

Background: The characteristics of mature contemporary rapid response systems are unclear.
Aim: To determine the patient characteristics, processes and outcomes, both in-hospital and post-discharge, of a well-established rapid response system in a tertiary adult hospital.
Methods: This is a prospective study of consecutive rapid response team (RRT) activations between 1 July and 25 November 2015. Variables included patient characteristics, timing, location and triggers of RRT activations, interventions undertaken, mortality and readmission status at 28 days post-discharge.
Results: A total of 1151 RRT activations was analysed (69.1 per 1000 admissions), involving 800 patients, of whom 81.5% were emergency admissions. A total of 351 (30.5%) activations comprised repeat activations for the same patient. Most activations (723; 62.8%) occurred out of hours, and 495 (43%) occurred within 48 h of admission. Hypotension, decreased level of consciousness and oxygen desaturation were the most common triggers. Advanced life support was undertaken in less than 7%; 198 (17.2%) responses led to transfer to higher-level care units. Acute resuscitation plans were noted for only 29.1% of RRT activations, with 80.3% stipulating supportive care only. A total of 103 (12.6%) patients died in hospital, equalling 14 deaths per 100 RRT activations. At 28 days, 150 (18.8%) patients had died, significantly more among those with multiple versus single RRT activations (24.9 vs 16.6%; odds ratio 1.66, 95% confidence interval 1.31–2.44; $P = 0.013$).
Conclusion: Relatively few RRT activations are associated with acute resuscitation plans, and most interventions during RRT responses are low level. The high rate of post-RRT deaths and transfers to higher-level care units calls for the prospective identification of such patients in targeting appropriate care.

Introduction

Rapid response systems (RRS) are enshrined as a national health service standard[1] and are widely implemented in hospitals throughout Australia and

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New Zealand. Such systems aim to rapidly identify clinically deteriorating patients (afferent limb) and activate appropriately trained teams (rapid response teams (RRT)) who provide resuscitative interventions (efferent limb), thereby preventing subsequent cardiac arrests and in-hospital deaths.[2] Whether RRS actually achieve these outcomes is still debated.[3–5] Multiple studies, including several systematic reviews, report mixed results with regards to overall in-hospital mortality.[6–11]

Protagonists of RRS argue that negative studies may reflect immaturity or insufficient cultural acceptance of RRS within study hospitals[12] and represent failures of implementation rather than of the concept itself. Others highlight the opportunity costs of assigning staff to RRS rosters, which intrudes on their other duties,[13] decisional conflicts around patient management between RRT and treating teams,[14] deskilling of ward staff in acute care[15] and the tension between appropriate patient-centred end-of-life care versus the potential for RRS to encourage inappropriately invasive and aggressive intervention.[16] In light of such debates, the activities and outcomes of contemporary RRS in Australian hospitals with mature and culturally accepted systems have been under-investigated.

Separate studies in the past have investigated various dimensions of RRS, such as patient profiles,[17,18] clinical triggers,[19,20] timing of RRS activation,[21,22] actions undertaken by RRT,[6,23–25] frequency of end-of-life decisions[26–28] and selected outcomes following RRT responses.[17] However, to our knowledge, there has been no recent Australian study of a well-embedded RRS that has measured all these variables concurrently and followed patient progress to discharge and beyond.

In this report, we detail patient characteristics, processes and outcomes, both in-hospital and post-discharge, of an RRS in a large tertiary adult hospital with a 5-year history of systematised hospital-wide patient surveillance and established RRS.

Methods

Study design

This was a prospective study of all consecutive RRT activations between 1 July and 25 November 2015 involving any patient admitted to, or receiving outpatient care at, the Princess Alexandra Hospital (PAH) in Brisbane, Australia. Data were collected on the total episodes of care, and patients were followed up to 28 days post-discharge.

Hospital characteristics and rapid response systems

Princess Alexandra Hospital is a 780-bed university-affiliated tertiary hospital for adult patients servicing a population of 600 000 in southeast Queensland. Clinical services comprise a wide range of medical and surgical subspecialties, including cardiothoracic surgery, neurosurgery, liver and kidney transplantation and major trauma.

The RRS has been in place since October 2009 and operates 24 h a day, 7 days a week, and covers all units of the hospital except the intensive care unit (ICU) and operating theatres (OT). The RRT, or 'code blue' team, is activated by a single-parameter trigger system based on bedside observation charts, which are colour-coded according to deteriorating thresholds of individual physiological parameters. There is no aggregate weighted scoring system for defining trigger thresholds based on multiple parameters. The standard criteria for RRT activation are as follows: threatened airway, systolic blood pressure <90 mmHg, heart rate >140 or <40 beats per min (bpm), oxygen saturations on pulse oximetry <90%, respiratory rate >36 or <8 per min, decrease in Glasgow Coma Scale by two points, prolonged or repeated seizures or any staff concerns. The RRT is comprised of a medical registrar (who is assigned team leader), a junior intensive care registrar, an intensive care outreach nurse, two junior doctors and two emergency department nurses with defibrillator and crash trolley. The team is activated by an urgent 'code blue' pager message, which provides ward location and bed number. The call can be triggered by any member of staff, although senior nurses assume primary responsibility. Activation of RRT calls occurs without delay once trigger criteria are breached and is not contingent on staff having first to make a request for patient review to attending medical teams or ward call medical officers. Quarterly audits of observation charts reveal that more than 90% of activation triggers are escalated appropriately with no appreciable delays. Following a completed RRT response, an intensive care outreach nurse reviews every patient within 8 h to assess clinical status and note compliance with RRT recommendations. Hospital policy dictates all patients deemed to be at risk of clinical deterioration should have an acute resuscitation plan (ARP) completed as soon as possible after admission with clearly stated ceilings of care.

Data collection

A standardised rapid response sheet was completed by ward staff during RRT calls. Routinely collected information comprised the reason for activating the RRT call, attending members of the RRT, observations performed, any treatment or interventions undertaken and immediate outcome of the RRT response. The intensive care outreach nurse collected the completed form, entered

any missing variables and entered the data into the hospital RRS database.

As a measure of illness severity and pre-RRT risk for clinical deterioration, the National Early Warning Score (NEWS)[29] was calculated retrospectively for each RRT activation using the algorithm depicted in Appendix I. Low risk was assigned a score of 0–4, intermediate risk a score of 5 or 6 or any extreme value for one or more trigger parameters and high risk a score ≥7.

The level of actions undertaken during each RRT response was classified as low level (medications and interventions routinely used in general wards), medium level (intravenous medications not routinely used in general wards (e.g. intravenous anti-arrhythmics) or requirement for cardiac monitoring) or high level (invasive or complex interventions normally reserved for intensive care or high dependency units). Using a classification system adapted from that used by other investigators,[30] the major intervention theme of each RRT response was classified as no care provided, education and expeditious care, escalation of care and end of life care.

In addition, medical records of each patient were reviewed to (i) extract data on medical comorbidities from which the Charlson comorbidity index was calculated, (ii) determine the existence and content of ARPs prior to RRT activation or formulated during or within 24 h after the RRT response and (iii) assign a clinical syndrome responsible for each RRT activation *post hoc*, consistent with previously described methods,[20] using pre-activation patient data from medical records combined with observations and actions taken during the RRT response.

The above data for each RRT activation were combined with demographic patient data obtained from the hospital administrative data system. This included admission date, length of stay (LOS), admission type (elective or emergency), admitting department (medical or surgical), transfers to other units within 24 h after RRT activation, principal and secondary discharge diagnoses, in-hospital death and discharge destination. Mortality and unplanned readmissions at 28 days were obtained from the Australian Death Registry and the Queensland Health Hospital Admitted Patients Database respectively.

Statistical analysis

Descriptive statistics were reported as mean and standard deviation (SD) for normally distributed continuous data or median and interquartile range (IQR) for non-normally distributed data. Comparisons between two categorical variables were performed using Chi-square or Fisher's exact test when appropriate, and odds ratios (OR) with 95% confidence intervals (CI) were reported. A comparison of continuous variables between two groups was performed using a *t*-test for normally distributed data and the Mann–Whitney test for non-normally distributed data. Analyses were performed using SPSS version 22, and statistical significance was denoted by $P < 0.05$.

Ethics approval

Ethics approval for the study was obtained from the PAH Human Research and Ethics Committee (HREC/15/QPAH/319). As routinely collected data on standard clinical care were being used, consent from individual patients was not deemed necessary.

Results

Rapid response team activations

Over the 6-month study period, there were 1151 RRT activations, of which 800 (69.5%) were for unique patients, the remaining 351 (30.5%) being repeated activations for the same patient. The median number of activations per patient was one (IQR = 1), with 15.4% of patients having two activations, 6.0% having three and 4.2% having four or more. There were on average 7.8 (SD ± 3.1) RRT activations per day, equating to 69.1 activations per 1000 admissions. There were 22 non-ICU, non-OT cardiac arrests, representing 1.2% of all RRT activations at a frequency of 1.3 per 1000 admissions.

The majority of activations occurred after 16.00 and before 08.00 (723; 62.8%) and on weekdays (805; 69.9%). There was no significant variation in the numbers of activations according to the day of the week, with a median of seven (IQR = 5) activations per weekday versus eight (IQR = 4) per weekend day. A total of 495 (43%) activations occurred within the first 48 h of admission, 143 (12.4%) between day two and four of admission and 513 (44.6%) after day four. The median time to RRT activation from day of admission was 3 days (IQR = 10).

Patient characteristics

Median age was 66.1 years (IQR = 24.8), with a range of 16–97 years. Most patients were male (468; 58.5%); 652 (81.5%) were admitted as emergencies; 415 (51.9%) were surgical patients, and 766 (95.8%) were classified at the time of the first RRT activation as receiving acute care.

The most common medical comorbidities were moderate to severe chronic kidney disease (defined as baseline estimated glomerular filtration rate <60 mL/min) affecting 239 (29.9%) patients, chronic pulmonary disease (219; 27.4%), ischaemic heart disease (202; 25.3%) and diabetes mellitus (193; 24.1%). The median Charlson comorbidity index (Table 1) was six (IQR = 6), with 285 (35.6%) patients having a very high score (score >7), 166 (20.8%) a high score (score 6, 7), 145 (18.1%) a medium score (score 4, 5) and 204 (25.5%) a low score (0–3).

RRT activation triggers

Trigger criteria for RRT activations are summarised in Table 2. Systolic blood pressure <90 mmHg was the most common trigger, occurring in 339 (29.5%) activations, followed by decreased Glasgow Coma Scale (n = 240; 20.9%) and oxygen saturations <90% (n = 227; 19.7%). Heart rate <40 bpm was the least frequent trigger, occurring in only 20 (1.7%) activations. Serious concerns of hospital staff featured in 175 (15.2%) activations and were the sole trigger in 92 (8%). Multiple triggers were noted in 217 (18.9%) activations. Of the 351 RRT activations involving patients with multiple RRT activations during their hospital stay, the RRT trigger criteria were altered in 12.2% of instances.

NEWS score

The median NEWS score at the time of RRT activation was 7 (IQR = 4), with 600 (52.1%) activations associated with high risk, 457 (39.7%) with medium risk and 94 (8.2%) with low risk.

RRT responses

The mean duration of RRT responses was 33.2 (SD ± 0.5) min. Investigations and interventions performed are summarised in Table 3. The most common actions were taking an electrocardiograph (65.8%), drawing venous blood samples for simple analyses (41.9%), administering an intravenous fluid bolus (29.6%), performing arterial blood gases (26.8%) and ordering a chest X-ray (24.8%). Advanced life support interventions comprising cardiopulmonary resuscitation, defibrillation and ventilatory assistance (bag and mask ventilation/endotracheal tube insertion/tracheostomy tube change) occurred in 1.7, 0.4 and 6.3% of responses respectively. The frequencies of each level of RRT intervention were none (21.1%), low level (62.3%), medium level (10.0%) and high level (6.6%). The frequencies of each theme were no care provided (14.0%), education and expeditious

Table 1 Comorbidity profile

Comorbidity	*n* (%)
Ischaemic heart disease	25.3% (202)
Congestive heart failure	20.0% (160)
Peripheral vascular disease	10.1% (81)
Cerebrovascular disease	13.1% (105)
Dementia	7.8% (62)
Chronic pulmonary disease	27.4% (219)
Moderate/severe chronic kidney disease	29.9% (239)
Chronic liver disease	7.1% (57)
Diabetes	24.1% (193)
Malignancy	9.1% (73)

Table 2 RRT activation triggers

Variable	*n* (%)
Systolic blood pressure <90 mmHg	29.5% (339)
Decreased GCS or loss of consciousness	20.9% (240)
SpO2 <90%	19.7% (227)
Heart rate >140	13.6% (156)
Heart rate <40	1.7% (20)
Respiratory rate >36	9.3% (107)
Respiratory rate <8	2.9% (33)
Seizure	6.5% (75)
Serious concern	15.2% (175)
Multiple triggers	18.9% (217)

GCS, Glasgow Coma Scale; RRT, rapid response teams.

Table 3 RRT actions

Action	*n* (%)
Investigations	
Arterial blood gas	26.8% (308)
Blood tests	41.9% (482)
Microbiological cultures	6.8% (78)
Chest X-ray	24.8% (286)
Electrocardiograph	65.8% (757)
Venous blood gas	6.1% (70)
Computerised tomographic scan	9.5% (109)
Ventilatory assistance	
Hi-flow oxygen	10.9% (125)
Oropharyngeal or nasopharyngeal airway	1.2% (14)
Bag and mask ventilation	3.7% (43)
Endotracheal tube	2.2% (25)
Tracheostomy tube change	0.4% (5)
Non-invasive ventilation	1.8% (21)
Circulatory intervention	
Intravenous access	18.3% (211)
Intravenous fluid bolus	29.6% (341)
Blood products	1.7% (19)
Anti-arrhythmic drugs	6.1% (70)
Cardiopulmonary resuscitation	1.7% (19)
Defibrillation	0.4% (5)
Cardioversion of supraventricular arrhythmias	0.4% (5)
Vasopressors	3.4% (39)

RRT, rapid response teams.

care (69.3%), escalation of care (14.7%) or end of life care (2.0%).

Acute resuscitation status

A total of 255 (22.2%) RRT activations involved patients who had an ARP completed prior to the activation. Of the 896 responses to patients without an ARP, 23 (2.6%) had an ARP completed during the response, and another 57 (6.4%) had an ARP completed within 24 h of the response. Of 335 ARPs that were completed, 269 (80.3%) were for supportive care (i.e. absence of resuscitative intervention), and 66 (19.7%) were for active care.

The level of intervention and theme of RRT actions undertaken during 255 responses to patients who had an ARP in place prior to the RRT activation are summarised in Table 4. Comparing patients with active versus supportive ARP status, the proportions of each group contained within each level of intervention or within each theme were not significantly different. This indicated a lack of concordance between the intensity of actions taken during the RRT response and the ARP status, irrespective of whether the latter was documented, or if it was, whether it stipulated active or supportive care.

Clinical syndromes responsible for RRT activations

The clinical syndromes responsible for each RRT activation that were assigned *post hoc* are listed in Table 5. Sepsis was most prevalent (11.9%) followed by fluid responsive hypotension secondary to dehydration (10.3%), transient decreased level of consciousness (8.1%), tachyarrhythmia (7.7%) and hypotension of unclear cause (7.0%).

Table 4 RRT actions for patients with pre-RRT activation ARP

	Active (n = 60) n (%)	Supportive (n = 195) n (%)
Level of intervention		
None	8 (13.3%)	35 (17.9%)
Low level	45 (75.0%)	142 (72.8%)
Medium level	6 (10.0%)	14 (7.2%)
High level	1 (1.7%)	4 (2.1%)
Major theme		
No care provided	6 (10.0%)	26 (13.3%)
Education and expeditious care	45 (75.0%)	137 (70.3%)
Escalation of care	9 (15.0%)	14 (7.2%)
End-of-life care	0 (0%)	18 (9.2%)

ARP, acute resuscitation plans; RRT, rapid response teams.

Table 5 Clinical syndrome responsible for RRT activation

Group	n (%)
Adverse drug reaction	39 (3.4%)
Arrhythmia: tachycardia	89 (7.7%)
Arrhythmia: bradycardia	17 (1.5%)
Cardiac arrest	22 (1.9%)
Decreased LOC: transient and unclear cause	93 (8.1%)
Decreased LOC: persistent and unclear cause	17 (1.5%)
Decreased LOC: intracranial pathology	34 (3.0%)
Decreased LOC: medication-related	11 (1.0%)
Hypotension: unclear cause	80 (7.0%)
Hypotension: fluid responsive/dehydration	118 (10.3%)
Hypotension: post-operative	13 (1.1%)
Hypotension: bleeding	17 (1.5%)
Hypotension: other cause	28 (2.4%)
Respiratory distress: aspiration	26 (2.3%)
Respiratory distress: other cause	82 (7.1%)
Respiratory distress: unclear cause	22 (1.9%)
Lower respiratory tract infection	42 (3.6%)
Pulmonary oedema	58 (5.0%)
Pulmonary embolism	7 (0.6%)
Seizure: self-limiting	48 (4.2%)
Seizure: terminated with medications	21 (1.8%)
Seizure: status epilepticus	9 (0.8%)
Sepsis	137 (11.9%)
Other	121 (10.5%)

RRT, rapid response teams.

Outcomes following RRT response

Transfer to high dependency units within 24 h

Transfer to the ICU followed 128 RRT responses (11.1%); transfers to the coronary care unit followed 39 (3.4%); transfers to respiratory high dependency unit followed 16 (1.4%), and transfers to OT followed 38 (3.3%). Transfer to any higher-care unit, including the OT, followed 198 (17.2%) of all RRT responses.

In-hospital mortality

In-hospital death occurred in 103 (12.6%) of 800 patients who activated RRT responses, which equates to 14 deaths for every 100 RRT activations. Patients who had multiple RRT activations during their admission tended to have higher in-hospital mortality compared to those with only one activation (16.1 vs 11.8%; OR 1.44, 95% CI 0.92–2.25; P = 0.117).

Discharge destination

Among 699 patients surviving to discharge, most (545; 78.0%) were discharged to their usual residence; 33 (4.7%) were placed in supported accommodation; 59 (8.4%) remained in-hospital at the conclusion of the study, and 62 (8.6%) were transferred to another hospital.

Length of stay

The median LOS of patients with at least one RRT activation was 11 (IQR = 20) days, with 9.3% having LOS <48 h, 26.8% having LOS 2–7 days, 40.3% with LOS 8–28 days and 23.8% with LOS >28 days.

Mortality at 28 days

At 28 days following admission, 150 (18.8%) of 800 patients had died, which equated to 21 deaths per 100 RRT activations. Mortality was significantly higher among patients with multiple RRT activations versus those with single activations (24.9 vs 16.6%; OR 1.66, 95% CI 1.31–2.44; $P = 0.013$).

Unplanned readmissions at 28 days post-discharge

Among 699 patients surviving to discharge, 270 (38.6%) had an unplanned readmission within 28 days of discharge, equating to 23 readmissions per 100 RRT activations.

Discussion

Overview of findings

This large prospective study of RRT activations yields several key findings. With regards to patient characteristics, more than a third were over the age of 70; more than 80% were emergency admissions, and more than half involved surgical patients. More than 90% were classified as medium to high risk of deterioration based on NEWS scores, although less than a quarter had ARPs completed, consistent with findings of a recent meta-analysis.[26] Close to half of all RRT activations occurred within the first 48 h of admission, with the majority involving emergency admissions, questioning whether early assessment and stabilisation was optimal. A third were repeat activations in the same patient, which suggests either refractory illness, insufficient escalation in care or failure to institute appropriate palliative measures.

With regards to RRT activations, the rate of 69.1 activations per 1000 admissions, averaging 8 per day, is in the upper range reported in previous studies[31,32] and well above what others have defined as a minimum rate indicative of a mature, responsive RRS.[12] It suggests, but does not confirm, a low rate of failure to activate RRT in the presence of activation triggers, which is to be the subject of further study. Two-thirds of activations occurred outside of normal working hours, and most occupied between 20 and 40 min of RRT time. Hypotension, decreased level of consciousness and oxygen desaturation were the most common triggers, although close to one in seven calls was activated by unspecified staff concerns. The clinical syndromes presumed to have necessitated the RRT activation varied in type, with sepsis, dehydration and tachyarrhythmia being the most common.

However, less than 10% of RRT responses involved the administration of advanced life support interventions, and less than 2% involved patients in cardiorespiratory arrest. In more than 80% of responses, the most common RRT actions were performing investigations, procuring intravenous access and administering intravenous fluids. The level of intervention was mostly classified as none or low level, and theme was mostly classified as no care or education and expedited care. However, one in seven RRT responses were followed by patient transfer to a higher-care unit within the following 24 h, suggesting a perceived need for closer monitoring and rapid access, if needed, to more invasive care.

Despite receiving an RRT response, just over one in eight patients died in hospital, and almost one in five was deceased by 28 days, with a 60% greater mortality risk in those with multiple versus single RRT activations. Among survivors, roughly half had a prolonged LOS (>14 days), and a third required an unplanned readmission within 28 days.

Implications for practice

Over the last 5 years, since the inception of RRS at the study hospital, the number of RRT activations per month has more than doubled, from 100 per month in 2010 to 240 per month in early 2015. This rate is likely to continue rising as a result of the growing numbers of multimorbid patients requiring hospital care who, in this study, were responsible for the majority of RRT activations. Over the same period, the hospital standardised mortality ratio (HSMR) ranged between 60 and 70, indicating better-than-average patient safety, which may be at least partly attributable to RRS-related patient surveillance and intervention. However, other hospital-wide reforms for decongesting the emergency department and optimising patient flow had been instituted prior to the study period, in association with a decrease in HSMR for emergency admissions.[33]

Four key themes arise from our study that have implications for quality improvement. First, despite the high comorbidity burden and high risk of clinical deterioration, less than a quarter of such patients had ARPs completed prior to calls, and only a small additional number had ARPs completed after the response or had their trigger criteria altered. Insufficient attention is being paid to determining resuscitation status prior to clinical

deterioration, and this may reflect a broader deficiency in advance care planning and appropriate end-of-life care involving patients with a limited prognosis.[34] It is likely that a significant number of RRT activations may be avoided by more explicit discussion and documentation of care goals and patient desire to avoid invasive intervention. Investigators have proposed that preventing unexpected deaths in patients without limitations of medical treatment, rather than all-cause death, may be a more appropriate indicator of RRS effectiveness.[35] Similar to our experience, the same authors noted how infrequently ARPs are formulated following RRT responses.[35]

Second, relatively few RRT activations involved patients who had severe clinical decompensation requiring advanced life support interventions. The majority of actions performed by RRT comprised low-level, non-invasive interventions. Interestingly, this was seen for all patients regardless of whether an ARP was completed beforehand or, if it had been completed, the stipulated ceilings of care. The low acuity of triggers activating RRT responses and the low intensity of most RRT responses may suggest overly sensitive activation thresholds that need to be recalibrated to more overt manifestations of serious deterioration. Whether current thresholds are compensating for low levels of confidence and skills, or insufficient staffing levels, in managing acutely ill patients on the part of ward staff needs to be considered. The absence of senior clinicians with medical expertise who can supervise and advise clinical teams on the management of clinically unstable patients at high risk of deterioration may be a further contributing factor.

Third, following RRT response, close to 20% of patients were subsequently transferred to a higher-care unit or OT, and despite best available care, almost a fifth of patients activating RRT died within 28 days. This raises the question as to whether RRT responses have temporarily delayed death because of irreversible illness in many of these patients or whether more intense post-RRT intervention targeted towards patients with active resuscitation status may reduce the incidence of such outcomes, particularly among those with multiple RRT activations. A clinical prediction rule that quantifies risk of death or other adverse outcomes following an RRT response would assist in this regard and is currently being developed and validated by the authors.

A final theme relates to interruptions to routine scheduled work of RRT staff, especially after-hours when staffing levels are at their lowest, and the potential to place other patients at risk of compromised care because of the absence of personnel involved in RRT responses elsewhere. The participation of seven professional staff in every RRT response, which consumed between 20 and 40 min, equates to between 2.3 and 4.6 full time-equivalent staff per day devoted to RRT activations. A single-site study to date has failed to detect suboptimal care or safety concerns resulting from staff involvement in RRS, although feedback indicated major disruption to normal work routines and staff inconvenience.[36] However, this single-site study had methodological limitations, chiefly recall bias, under-reporting of major incidents and a low RRT activation rate. Whether two-tier response systems (attending teams or ward call staff first review patients not suffering major or catastrophic clinical deterioration followed by full RRT response if critically ill or failed tier one response)[37] may be more efficient of personnel time yet yield equivalent or better patient outcomes is yet to be determined in clinical trials. One very recent study suggests the reverse, with more sensitive triggers combined with a two-tier response system leading to an 82% increase in RRT calls and a 41% increase in ICU admissions, with no change in rates of death or cardiac arrests.[38] This potential limitation of RRS, as well as others, has been described by us[39] and endorsed by other investigators,[40] indicating the need for more research into how RRS can be rendered more effective and efficient.

Conclusion

This detailed descriptive study of a mature and contemporary RRS in a large tertiary adult hospital highlights the low frequency of ARPs despite a high comorbidity burden among patients activating RRT. Additionally, for a critical care-based RRS, the level of intervention undertaken during the majority of RRT responses was relatively low and may suggest activation thresholds that are too sensitive. The staff and resource requirements of a mature RRS are not inconsiderable, and their effects on other aspects of care remain undetermined. Prospective identification of patients who are at a higher risk of dying or being transferred to higher acuity areas following an RRT response may assist in targeting such patients with interventions that are more or less intensive, as deemed appropriate by treating clinical teams.

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Appendix I

Table A1. NEWS scores

Parameter							
	3	2	1	0	1	2	3
Respiratory rate	≤8		9–11	12–20		21–24	≥25
Oxygen saturations	≤91	92–93	94–95	≥96			
Supplement oxygen		Yes		No			
Temperature	≤35		35.1–36	36.1–38	38.1–39	≥39.1	
Systolic blood pressure	≤90	91–100	101–110	111–219			≥220
Heart rate	≤40		41–50	51–90	91–110	111–130	≥131
Level of consciousness				A			V, P, or U
Clinical risk derivation							
Low	An aggregate NEWS of 1–5						
Medium	An aggregate NEWS of 5–6 OR An extreme variation in an individual physiological parameter: – Respiratory rate <8 or >25 – Oxygen saturations <91 – Temperature <35.0 – Systolic blood pressure <90 or >220 – Heart rate <40 or >131 – Level of consciousness: verbal, pain, unresponsive						
High	An aggregate NEWS of 7 or more						

A, awake; NEWS, National Early Warning Score; P, response to pain; U, unresponsive; V, responsive to verbal commands.

Inpatient healthcare utilisation in patients with alcoholic liver disease: what are the costs and outcomes?

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Key words
liver disease, alcoholic, alcohol abuse, mortality, delivery of healthcare, healthcare economics and organisation.

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Abstract

Background: Alcoholic liver disease (ALD) carries a significant cost burden and often leads to inpatient care. It is unclear whether inpatient care for ALD is any more costly than admission for other reasons.

Aims: To compare the costs and outcomes of inpatient care for ALD to two groups: a control group of matched cases admitted in the same time frame and people admitted for other chronic liver diseases (CLD).

Methods: All admissions for ALD and other CLD in a 3-month period were retrospectively identified. Five randomly identified gender- and age-matched contemporaneously admitted controls were allocated. Length of stay (LoS), mortality, inpatient costs, blood product utilisation and discharge destination were compared.

Results: Of the 71 admissions due to CLD, ALD was the most frequent cause (53/71, 75%). ALD admissions cost more (median $10 100 vs $5294; $P = 0.0012$) and had greater LoS (median LoS 7.2 days (interquartile range (IQR) 0.2–40.7)) than controls (2.6 days (IQR 1.1–6.8); $P = 0.0001$). A larger proportion of the ALD cohort required blood transfusion and had a higher mortality than controls (24.5 vs 6.4%, $P = 0.002$ and 13.2 vs 0.2%; $P < 0.0001$ respectively). Self-discharge was more common in the ALD group (13.2 vs 1.1%, $P < 0.0001$).

Conclusions: ALD inpatient hospital admissions have greater median total cost, longer LoS, greater blood product utilisation, higher mortality and greater rate of discharge against medical advice than age- and gender-matched controls. These data emphasise the large inpatient care burden, high mortality and suboptimal engagement in those with ALD, which justifies the more active provision of services for ALD.

Introduction

Alcoholic liver disease (ALD) is one of the leading causes of chronic liver disease (CLD) in developed countries and is said to have a high burden of cost. The consumption of alcohol is increasing among adults in Australia, including to hazardous levels, and this has led to an increase in the incidence of ALD.[1] ALD often leads to cirrhosis and its complications, which frequently lead to hospitalisation. The cost of inpatient care for ALD, however, is not well characterised, and it is unclear whether it is greater than for other CLD or for others requiring inpatient care in general.

Furthermore, an increasing proportion of Australian hospital separations for liver disease are alcohol-related,[2] highlighting the importance of examining this condition not only from the point of view of clinical outcomes but also the healthcare utilisation and planning for resource allocation. It affects patients at a younger age than many other chronic illnesses, with hospital admissions as a result of decompensated cirrhosis frequently occurring in patients in their 40s–50s. We sought to clarify the cost and impact of ALD in the setting of a non-transplant tertiary hospital as compared with contemporaneously matched controls.

Methods

A retrospective case-controlled cohort study was carried out at Royal Adelaide Hospital, a metropolitan tertiary hospital with 650 inpatient beds in South Australia. Admissions pertaining to ALD were identified by the case coding unit using discharge data (International Statistical

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Table 1 ICD-10-AM codings for alcoholic liver disease (ALD)

Code	Diagnosis
K70.0	Alcoholic fatty liver
K70.1	Alcoholic hepatitis
K70.2	Alcoholic fibrosis and sclerosis of liver
K70.3	Alcoholic cirrhosis of liver, alcoholic cirrhosis NOS
K70.4	Alcoholic hepatic failure
K70.9	ALD unspecified

ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification; NOS, not otherwise specified.

Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification, ICD-10-AM)[3] over a 3-month period: 1 January to 31 March 2010. Admissions with a primary or secondary diagnosis pertaining to code K70 (ALD) were identified (Table 1). The electronic separation summaries of these cases were then examined by the lead author (KDW) to ascertain whether ALD was actually a contributing factor to the admission. Admissions in which ALD was recorded only as a comorbidity rather than a causal factor in the admission were excluded. In cases where this was unclear, a second gastroenterologist (JMA) independently assessed the notes. In all conflicts, the decision regarding the contribution of ALD was unanimous. Cases with other concomitant CLD, such as hepatitis B or C, were included, as long as ALD was judged to be a significant contributing factor.

Controls were created by randomly identifying and allocating five age-matched and gender-matched admissions from all specialties from the same time period for each case using a computer algorithm by the Casemix unit, who were not involved in patient care.[4,5] A large control group was selected (i.e. five control admissions per ALD admission) to allow a general representation of the types of diagnoses present among patients of similar age and gender. Control admission could not have a code pertaining to ALD (Table 1), and the separation summary was interrogated for each control to ensure ALD was not contributory to the admission. Where any control was excluded, a new control was randomly identified, assigned and interrogated as above.

In addition, admissions during this time period for other CLD were identified using the appropriate ICD-10-AM code: hepatitis B (Z22.51), hepatitis C (Z22.52), hereditary haemachromatosis (E83.1), primary biliary cirrhosis (K74.3), non-alcoholic fatty liver disease (NAFLD) (K76.0), autoimmune hepatitis (Z22.52), alpha-1 antitrypsin deficiency (E88.0) and cirrhosis-unspecified (K74.6). Again, the separation summary for each admission was interrogated, and only those admissions attributable to CLD were included. It was noted if patients with a CLD had concomitant ALD.

For each of the ALD cases, controls and other CLD cases, various data were obtained: gender, age, admitting specialty, cost of admission, length of stay (LoS), discharge destination and mortality during admission. With regards to the cost of inpatient admission, a total cost was calculated from costs of individual categories according to standard local practice at the Casemix and Clinical Costing Unit at Royal Adelaide Hospital as per previously published methodology.[4,5] These included salaries for healthcare staff, hospital equipment and consumables and other overheads, medications, operating theatre/recovery costs, imaging and pathology costs, intensive care and coronary care unit costs and, finally, teaching costs. The use of blood products was also ascertained directly from the hospital blood transfusion service, and the proportion of admissions requiring a red blood cell transfusion was calculated, as well as the number of units.

The primary outcome was the cost of admissions due to ALD compared with controls. Secondary outcomes were comparative LoS, discharge destination, blood product utilisation and mortality. Comparisons were also made between admissions due to ALD and admissions due to other forms of CLD.

For a comparison of nonparametric continuous variables, such as admission costs and LoS, the Mann–Whitney test was applied. For a comparison between categorical variables, such as discharge destination, the chi-square test (Fisher's exact test) was applied. Proportions (such as mortality) were also compared using the chi-square test. For survival analysis, Kaplan–Meier curves were generated, with censorship at the time point of patient discharge for each admission, and a log-rank (Mantel–Cox) test was performed to evaluate statistical significance. The statistical software packages used were STATA/SE version 12.0 (Statcorp, College Station, TX, USA) and GraphpadPrism version 7.0a for MAC OS X (GraphPad Software, La Jolla, San Diego, CA, USA).

As this was a retrospective chart review, specific ethical review and individual patient consent were not judged to be necessary according to the National Health and Medical Research Council (NHMRC) principles covering clinical audits.

Results

Alcoholic liver disease admissions

A total of 83 admission cases was identified with a code pertaining to ALD. Of these, 53 admissions were judged to have ALD as a major contributing factor to the admission. The 30 patients excluded were because of their being admitted with other medical diagnoses, and ALD was listed as a comorbidity but did not play a causal role

Table 2 Admitting specialty according to cases versus controls

Admitting specialty	ALD (%), n = 53	Controls (%), n = 265
Gastroenterology	64	1.5
General medicine	26	10.9
Orthopaedics	4	7.2
Emergency admission	4	6.8
Renal medicine	2	2.6
General surgery	0	12.1
Cardiology	0	10.6
Psychiatry	0	7.2
Urology	0	6.4
Plastic surgery	0	4.9
Other unit (n < 10)	0	29.8

ALD, alcoholic liver disease.

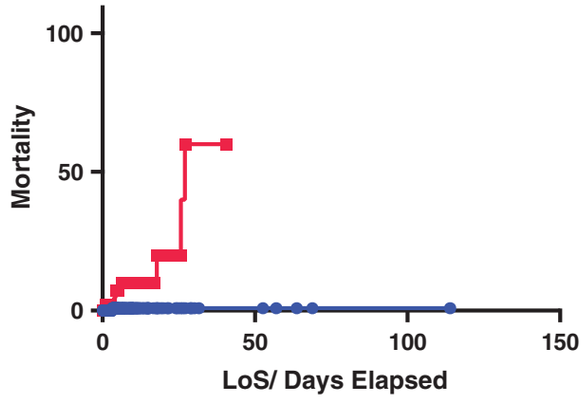

Figure 1 Kaplan–Meier survival curve demonstrating increased mortality of patients with alcoholic liver disease (ALD) compared with controls. Each event marks either a death or censorship because of discharge of a living patient. LoS, length of stay; P < 0.0001. (—■—), ALD; (—●—), control.

in the admission. Admission diagnoses in the 53 ALD cases included alcoholic hepatitis, ascites, variceal haemorrhage and encephalopathy; 265 controls were assigned. The median age of cases and controls was 54 years (range: 25–79 years), and 68% were male. Two thirds of ALD cases were admitted under gastroenterology, compared with only 1.5% of control cases. The major specialties under which control patients were admitted were general medicine, general surgery and cardiology, at roughly 10–12% each (Table 2).

A total of 46 patients accounted for the 53 ALD admissions. Thus, 41 patients were admitted for ALD on a single occasion, 3 patients had one readmission (2 ALD admissions each), and 2 patients had two readmissions (3 ALD admissions each). There were no readmissions included in the control group; hence, there were 265 unique control patients.

Of the 53 ALD admissions, 13 had an additional coexisting CLD – 10 with chronic hepatitis C (HCV) and 3 with chronic hepatitis B (HBV).

The median cost of admission because of ALD ($10 100, interquartile range (IQR) $4381–$16 996) was almost twice that of control admissions ($5294, IQR $2527–$10 806; P = 0.0012). This was consistent with a longer median LoS for ALD admissions (7.2 days, IQR 2.1–12.9) compared with controls (2.6 days, IQR 1.1–6.8, P = 0.0001). There was no difference between the daily cost of admission of ALD cases and controls (median cost per day for ALD ($1588.30, IQR $1152.14–$2010.46) vs controls ($1844.20, IQR 1236.11–2858.39; P = 0.1086)).

A total of 12 of 53 (22.6%) ALD admissions contained a gastrointestinal bleeding diagnosis, the majority of which were because of portal hypertension. Correspondingly, there was a significantly greater proportion of patients receiving blood products in the ALD group as compared with controls (13/53 (24.5%) ALD vs 17/265 (6.4%) controls, P = 0.002). However, in those receiving blood products, there was no difference in the number of units given per admission between ALD and control admissions (3.9 units in each group, P = ns). In two ALD cases and one control case, the number of units received was unknown.

There was a significantly higher mortality in the ALD admission group (7/53, 13.2%) compared with controls (1/265, 0.4%; P < 0.0001; Fig. 1). Median survival in the ALD group was 27 days. Due to the low incidence of deaths (n = 1) in the control group, median survival for the control group was undefined. In addition, there was a difference in discharge destination, with a significantly greater rate of self-discharge in the ALD group (7/53, 13.2%) compared with controls (3/265, 1.1%; P < 0.0001) (Fig. 2).

Other chronic liver diseases

During the same time period, there were 457 admissions in which a CLD was coded (Table 3). Of the 71 admissions with CLD as a contributing factor, ALD was an underlying diagnosis in the majority (53/71, 75%), followed by HCV (19/71, 27%). There were 182 admissions with HCV coded, but only a minority of these admissions were actually due to HCV. Likewise, 26 admissions during this time period contained a coding for HBV, but only 3 were attributable to liver disease. Although there were 103 admissions with 'hereditary haemochromatosis' coded, the vast majority (n = 99) were for scheduled venesection, with only three actually because of liver disease.

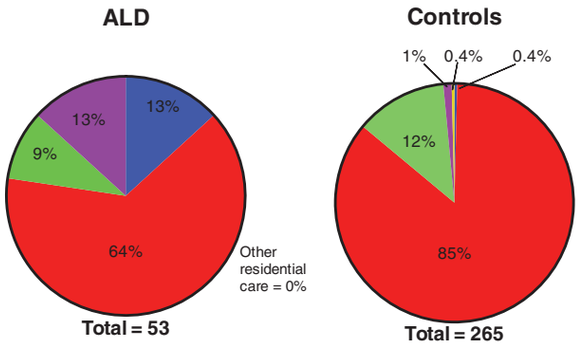

Figure 2 Discharge destination of alcoholic liver disease (ALD) admissions and control admissions. Note: rounded to nearest percentage; hence, although ALD pie segments add up to 99%, if using true percentages, the sum is 100%. Discharge destinations: (▬), died; (▬), home; (▬), other hospital; (▬), self-discharge; (▬), other residential care.

Table 3 Admissions attributable to chronic liver disease (CLD)†

Type of CLD	Admissions with this coding‡ (*n*), (*n* = 457)	Admissions due to CLD‡ (*n* (%)), (*n* = 71)
ALD	83	53 (75)
Hepatitis C	182	19 (27)
Hepatitis B	26	3 (4)
Hereditary haemachromatosis§	103	3§ (4)
Non-alcoholic fatty liver disease	6	2 (3)
Autoimmune hepatitis	2	2 (3)
Cirrhosis-unspecified	17	1 (1)
Alpha-1-antitrypsin deficiency	38	0 (0)
Primary biliary cirrhosis¶	0	0 (0)

†Note that there were 71 admissions attributable to CLD, and in some admissions, there were more than one underlying CLD as a contributing factor (e.g. ALD and hepatitis C); hence, the sum of the numbers in the final column come to greater than 71/100%. ‡Within study time period. §These three admissions were actually because of a patient being admitted three times with secondary hepatic haemosiderosis in association with Budd–Chiari, and the coding was incorrect. ¶Please note, the code for this disease was 'primary biliary cirrhosis', but the authors recognise the recently changed name as 'primary biliary cholangitis'. ALD, alcoholic liver disease.

Moreover, all three of these admissions occurred in a single patient with 'hereditary haemachromatosis' coded, yet they were actually because of secondary hepatic haemosiderosis in association with Budd–Chiari syndrome.

The median age for admissions due to HCV (54 years, range: 35–82) was the same as in both ALD and controls (54 years, range: 25–79), with a similar majority of males (HCV – 84% male, ALD/controls – 68% males). Due to the low numbers of admissions as a result of other CLDs, the demographics were not statistically compared, nor were costings compared to the ALD cohort.

When a patient was admitted because of their CLD as a contributing factor, the mortality rate varied. A total of 2 of 3 (67%) HBV admissions resulted in mortality, but both of these patients also had comorbid ALD; 2 of 19 (11%) HCV admissions resulted in death, but again, both these patients also had ALD. These four deaths were therefore included in the outcomes of ALD admissions. There were no deaths because of admissions for any other CLD without coexistent ALD.

Discussion

This study demonstrates that the cost of admission due to ALD is significant, it being almost double that of admissions for other reasons in a mixed cohort of age- and gender-matched controls. Most of this excess cost is because of a longer LoS. These data raise significant concerns for efficient healthcare utilisation and resource allocation. Moreover, they are of an increasing importance as this preventable condition is increasing in prevalence, with a recent Australian study showing that admissions due to ALD increased by 20% between 1993 and 2005.[6]

Alcohol abuse and its associated health problems are a major concern for Australia. Approximately one-third of Australians drink at levels above those recommended as safe alcohol consumption by NHMRC.[7]

Furthermore, over 3000 lives are lost each year in Australia because of high-risk alcohol consumption, and the leading cause of alcohol-related deaths in Australia is because of cirrhosis (approximately 21%), followed by alcohol dependence and road traffic accidents.[8] Consistent with this, we found a startlingly high mortality rate for admissions because of ALD, especially for a relatively young median age of 54 years (13.2% in ALD vs 0.4% in matched controls). Whilst there was a significant mortality rate in admissions where HCV or HBV was coded (66.7 and 10.5% respectively), all of these patients also had ALD, and it is impossible to determine the contribution of each condition separately on mortality.

Mortality from ALD is a significant issue all around the world. In Europe, the mortality rate varies from 3 to 47 per 100 000 in men (slightly lower in women).[9] In the United Kingdom, it has been identified that while mortality rates are going down for most chronic medical conditions, such as ischaemic heart disease, diabetes and cancer, CLD is the glaring outlier, with hospital admission and mortality rates consistently rising over the last

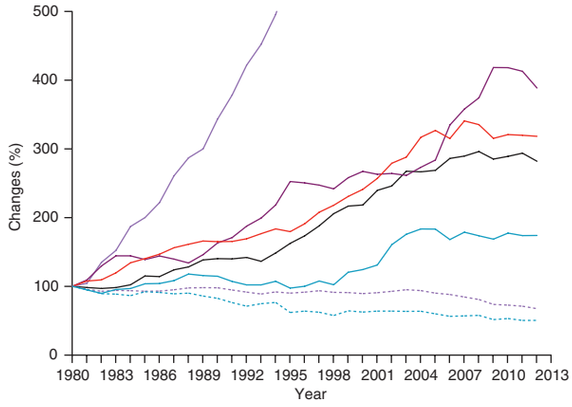

Figure 3 Standardised UK mortality rate data of diseases of various systems of the body. Whilst the mortality of most diseases is gradually declining over time, mortality due to liver disease is increasing at a significant rate. Data were normalised to 100% in 1970, and subsequent trends were plotted using the software Statistical Package for the Social Sciences. Data are from the WHO-HFA database. Reproduced from Williams *et al.*,[10] with permission. (——), Alcohol-related liver deaths in England and Wales; (——), white spirits consumption; (------), whisky consumption; (——), cider consumption; (——), wine consumption; (------), total lager or beer consumption; (——), packaged strong lager consumption.

50 years, and three quarters of deaths from CLD occurring because of alcohol excess (Fig. 3).[10]

Our mortality data differ from a recent report commissioned by the Gastroenterology Society of Australia (GESA), which found hepatitis C, closely followed by NAFLD, to be the leading cause of death among patients with CLD in Australia.[11] The third was hepatocellular cancer (HCC), and ALD was considerably down the list at fourth. Additionally, recent figures from the Australian Institute of Health and Welfare (AIHW) suggest that 38% of CLD hospital admissions are because of ALD.[12] There are several reasons for the disparity between the GESA report/AIHW figures and our data, which suggest ALD as the most frequent cause of both hospital admissions because of CLD and inpatient mortality because of CLD. The GESA report data mostly rely on estimates from a paucity of published literature on the epidemiology of various liver diseases in Australia. It is likely that a large portion of HCV patients had alcohol as a co-factor in their disease,[13] and indeed, it is known that excess alcohol is an independent risk factor for progression to cirrhosis in those with HCV.[14,15] A recent epidemiological study observed, consistent with our findings, that alcohol consumption, but not HCV, was significantly associated with CLD-related mortality.[16] Additionally, it is our experience that patients with HCV cirrhosis are admitted to hospital infrequently, except for elective endoscopies and transplant assessment workup. Those patients with NAFLD in the GESA report are more likely to have died of other causes (such as malignancy and cardiovascular disease, given their known comorbidities related to obesity and diabetes) rather than of their liver disease (as is well known from the literature),[17–19] and a large portion of patients with HCC have underlying ALD, a known leading risk factor. Lastly, the Australia and New Zealand Liver Transplant Registry Data support ALD as a leading indication for adult liver transplantation – 22.9% HCV, followed by 12.4% ALD, bearing in mind that a large proportion of ALD patients are not considered for transplantation because of ongoing alcohol consumption, with metabolic causes (such as NAFLD) only 4.5%.[20] So, whilst our study differs from the GESA and AIHW data, given the scarcity of accurate Australian CLD epidemiologic data and the reliance of the GESA report on estimates, it is important also to acknowledge our findings from real-world admission data in a major metropolitan hospital. We believe our figures are real-life data that reflect day-to-day clinical experience that ALD actually represents the major cause of inpatient CLD admissions.

Our study also showed that admissions due to ALD had a relatively high use of blood products – 24.5% ALD admissions resulted in a red blood cell transfusion, compared with only 6.4% control admissions. This reflects the common occurrence of gastrointestinal bleeding among this patient cohort. Blood products are a precious resource, and this represents another non-economic impact of this preventable disease.

So what should be done to improve this situation of increasing prevalence of alcohol abuse and high mortality and health resource utilisation of admissions due to of ALD? A recent comprehensive report examined factors associated with deaths due to ALD in Great Britain. They identified that 70% of patients had been in hospital within the previous 2 years, and they recommended that readmission with an alcohol-related diagnosis should trigger prompt referral to an appropriate support service, and a system should be in place for this. Across the hospitals, they also identified a low availability of consultant hepatologists (in only 28% hospitals), a paucity of multidisciplinary alcohol care teams (23% of hospitals) and a lack of existence of guidelines/treatment pathways for ALD (roughly half of the hospitals). These factors may represent contributing reasons for the poor outcomes of patients admitted with ALD and highlight areas for improvement. Indeed, these parameters could be examined in Australian hospitals, with a focus on these and other areas highlighted in a recent joint position

statement released by various British Gastroenterology and Hepatology associations.[10] Social supports are also important in the care planning of inpatients with ALD, as reflected by the high rate of self-discharge seen in this study.

Looking at broader preventive measures, there are many possible preventive measures that may be implemented, as endorsed by the Royal Australasian College of Physicians in their Alcohol Policy.[21] These include alcohol taxation reform, such as minimum unit pricing, better regulation of alcohol advertising, stricter regulation of licensed premises, enhanced training of physicians in alcohol/addiction medicine, better treatment services for patients with alcohol addiction and further funding opportunities for alcohol-related medical research. It has been demonstrated previously that effective alcohol policy measures reduce alcohol mortality, including mortality from liver disease.[22] However, more funding is needed from a government level – both federal and state – for alcohol and other drug resources as, currently, there is a high unmet need.[23] We suggest that establishing effective alcohol reduction measures and policy should receive the same priority and funding as expanding HCV treatments.

A limitation of the study is its retrospective nature and possible errors made in relying on ICD-codings, case notes and electronic separation summaries, although this is unlikely to be a significant issue as every attempt was made to avoid misclassification by careful interrogation of cases by one to two clinicians. With regards to costs, there were some cases of short admissions in controls of less than 1 day – 52 of 265 (19.6%) controls compared with 5 of 53 (9.4%) of ALD admissions. This may have potentially skewed the costs higher with regards to the ALD compared with controls, but a difference of 10% is unlikely to have had enough impact to cause ALD admissions to cost double that of control admissions.

Another limitation is the small sample size of only 53 admissions due to ALD. However, a strength, compared with large database-centred epidemiology studies, is the rigorous attention by a clinician that the admissions were classified correctly, and indeed, despite the small numbers, clinically relevant and statistically significant findings were made.

Conclusion

In conclusion, this study highlights the health economic burden of ALD in Australian hospitals, particularly in the demographic of middle-aged males. The cost of admission due to this condition was higher than inpatient care for other reasons, and mortality rates were also disproportionately high. Increased resources for patients with ALD may help to improve cost and outcomes in these patients, and this, together with effective strategies to prevent ALD, should become an increased public health focus in Australia.

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Incidence of cutaneous squamous cell carcinoma in a New Zealand population of chronic lymphocytic leukaemia patients

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Key words
chronic lymphocytic leukaemia, skin cancer, squamous cell carcinoma, incidence.

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Abstract

Background: Chronic lymphocytic leukaemia (CLL) is associated with an increased incidence and aggressiveness of skin cancers, particularly cutaneous squamous cell carcinoma (cSCC), but little is known about cSCC incidence in Australasian CLL patients.
Aim: In this retrospective study, we analysed the incidence of cSCC in patients seen at a tertiary hospital in New Zealand (NZ).
Methods: We retrospectively assessed the clinical history and histology data of CLL patients (n = 371) who presented to the Haematology Department, Christchurch Hospital, NZ during the period 1996–2015. Baseline characteristics, incidence of second cancers, treatment details and overall survival were analysed.
Results: During follow-up (median = 11.8 years), 221 second cancers were recorded in 88 patients. Of these cancers, 185 were cSCC, removed from 61 patients. In 56% of these patients, >1 cSCC was removed, and the majority of cSCC occurred following the treatment for CLL. The cumulative incidence of a first cSCC was 11% at 5 years, whereas the cumulative incidence of a subsequent cSCC was 88% at 5 years. The incidence of cSCC in male patients was threefold higher than that reported for the general NZ population.
Conclusion: NZ CLL patients have a high incidence of cSCC relative to the levels observed in the general population, which are themselves among the highest in the world. The careful monitoring of CLL patients is warranted, particularly those who have a progressive disease or have had a first cSCC removed.

Introduction

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia in the Western world. Although CLL typically follows an indolent course, it is well established that these patients have a greater than twofold increased risk of developing a second malignancy.[1–13] These malignancies often have an unusually aggressive nature.[7,14–19] Skin cancers, particularly non-melanoma skin cancer (NMSC), are the most common second malignancy observed, with several studies reporting a five- to eightfold increased risk of NMSC development.[2,7–13] This increased incidence and aggressiveness is thought to reflect, at least in part, immunosuppression associated with CLL.[20]

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It is now well established that ultraviolet (UV) radiation exposure and immunosuppression are key risk factors for the development of skin cancers, of which NMSC is the predominant type. The majority of NMSC-associated morbidity and mortality, in both the general and immunosuppressed populations, is attributable to cutaneous squamous cell carcinoma (cSCC). Studies in the Northern Hemisphere have reported that CLL patients have an increased incidence of cSCC.[7,12,13] Studies in both the Northern Hemisphere and Australasia have similarly reported that CLL-associated cSCC have a more aggressive nature, as reflected in higher levels of recurrence, metastasis and cSCC-related mortality.[7,9,17–19] The impact of this on the overall survival (OS) of CLL patients with skin cancer (predominantly cSCC) was emphasised by a recent report showing that the mortality was as high from skin cancer as from CLL.[16]

New Zealand (NZ) and Australia have high levels of UV exposure, relative to the population skin type, and,

consequently, have among the highest rates of skin cancer in the world. Data obtained from Australasian renal transplant recipients (RTR)[21,22] suggest that the cumulative effects of immunosuppression and high background population levels of skin cancer should result in an elevated incidence of skin cancers in Australasian CLL patients. However, the magnitude of this increased incidence is unclear. Similarly, fewer data are available on the frequency or timing of cSCC occurrence in individual CLL patients.

The development of second cancers in CLL patients, particularly skin cancers, represents a considerable clinical burden. However, fewer data are available regarding the incidence of skin cancers in CLL patients from Australia or NZ. We undertook a hospital-based survey, aiming to provide 'real-life' information of value to patients, their doctors and the health systems in which they are treated. We have studied the incidence of second cancers in patients with CLL who presented to the Haematology Department of Christchurch, NZ, between 1996 and 2015.

Methods

This study was approved by the Central Health and Disability Ethics Committee (NZ).

CLL patients, who presented to the Haematology Department of Christchurch Hospital between 1996 and 2015, were identified using the Haematology Department databases. Information on CLL diagnosis, treatment and outcomes, together with details of second cancer occurrence, were obtained through a review of written and electronic hospital records.

All malignant, non-skin cancers were included. Skin cancers included in the study were malignant melanoma (MM) and NMSC. Basal cell carcinomas were excluded because of their low risk of poor outcomes. cSCC were staged using the Brigham and Women's Hospital (BWH) system, where categories T1 and T2a are considered low risk, and categories T2b and T3 are considered high risk.[23]

For the analysis of second cancer incidence, duration of follow-up was calculated from the date of CLL diagnosis to the date of either (i) first diagnosis of a second cancer, (ii) the last follow-up (as defined by patient records) or (iii) death. With respect to the incidence of skin cancers, multiple cancers removed at the same time were treated as a single event. Cumulative incidence and OS was estimated using the Kaplan–Meier method. Median follow-up times were calculated using the Kaplan–Meier method, with the meaning of the status indicator reversed.[24]

Incidence rates for cSCC were determined for each age band based on the number of patients who had a first cSCC removed and the total person years. Incidence was expressed as events per 100 000 person years, and confidence intervals (CI) were calculated based on the gamma distribution.[25] Data for the NZ male population were obtained from previously published data.[26]

Results

Patient characteristics

A cohort of 371 CLL patients who presented at the Christchurch Hospital Haematology Department in the years 1996–2015 was identified following a review of department records. Median age at diagnosis was 67 years, and the majority of patients were male, Binet stage A and $CD38^{neg}$ (Table 1). During follow-up (median = 11.8 years), 50% of patients received treatment for CLL, and a total of 191 deaths occurred, with a median OS = 10.1 years.

Second malignancies

Over the period of follow-up, 221 second cancers were recorded in 88 patients. Using the occurrence of the first second cancer as the end-point, the cumulative incidence at 5 years was 16% and at 10 years was 33% (Table 2, Fig. 1). The predominant type of second cancer was invasive skin cancer. These malignancies were present in 74% of patients with second cancers and made up 90% of the recorded second cancers. Relatively few non-skin cancers were recorded, with lung and colon cancer being the most common types.

Skin cancer

A total of 65 patients had invasive skin cancer. The predominant type was cSCC, which occurred in 61 of these patients (Table 2). A small number of patients (n = 5) had MM removed; three of five of these were metastatic, and both cSCC and MM were removed at different times in one patient. The rare aggressive skin cancers Merkel cell carcinoma (MCC, n = 1) and sebaceous gland carcinoma (SGC, n = 2) occurred in three patients, and in each of those patients, cSCC were also removed.

A total of 185 cSCC was removed from 61 patients (Table 2). Relative to those patients in whom a cSCC did not occur, a significantly higher proportion of these patients received treatment for CLL during follow-up. At the time of diagnosis, a significantly higher proportion of these patients was male, aged >67 years or Binet stage B/C (Table 1). The median age at the time of first cSCC was 75 years (range: 51–93 years, data not shown), and for those patients, the median time from CLL diagnosis

Table 1 Characteristics of chronic lymphocytic leukaemia (CLL) patients

	Patient grouping			
		cSCC occurrence during FU		
Characteristic†	All	No	Yes	*P*‡
Patient number	371	310	61	
Age				
Median	67	66	71	
Range	35–97	35–97	47–91	
Mortality				
Deaths	191	158	33	
Median FU, years (95% CI)	11.8 (10.8–12.8)	11.4 (10.2–12.6)	11.8 (11.5–12.12)	
Median OS, years (95% CI)	10.1 (7.8–12.3)	10.1 (7.6–12.6)	10.8 (6.1–15.4)	
Male (%)	66%	62%	82%	0.003*
Binet B, C (%)	28%	25%	39%	0.023*
$CD38^{pos}$ (%)	34%	35%	29%	0.64
Received subsequent treatment for CLL (%)§	50%	47%	67%	0.003*
Age >67	49%	46%	62%	0.019*

*These values are statistically significant ($P < 0.05$). †Age, Binet stage and CD38 as at diagnosis. ‡The significance of differences between $cSCC^{neg}$ and $cSCC^{pos}$ patients was determined by Chi-squared statistic. §Treatment received at any time during follow-up. CI, confidence interval; cSCC, cutaneous squamous cell carcinoma; FU, follow-up; OS, overall survival.

to the occurrence of the first cSCC was 3.8 years (Fig. 2a). The majority of these patients ($n = 31$, 56%) had >1 cSCC removed, with 13 (21%) having ≥4 removed (Fig. 2b). In six patients, metastatic cSCC was recorded. As the majority of patients with a recorded cSCC also received treatment for CLL during follow-up, the temporal association between these events was analysed (Fig. 2c). In the majority of patients (>85%), the cSCC occurred following treatment. In the remaining patients, the cSCC preceded treatment by less than 6 months, resulting in a median interval of 1.7 years post-treatment.

Using the occurrence of the first cSCC as the endpoint, the cumulative incidence at 5 years was 11% and at 10 years was 23% (Fig. 3). Analysis of the cumulative incidence of a second cSCC indicated that virtually all patients who develop a cSCC subsequently develop another cSCC. From the time of the first recorded cSCC, the median time to the development of a second was 29 months (95% CI 12–46 months), and the cumulative incidence at 5 years was 88%.

Table 2 Second cancer type and number

	Number of patients (%)	Number of cancers (%)
All cancers	88 (100%)	221 (100%)
Non-skin cancers		
Total	23 (26%)	23 (10%)
Colon	4	
Lung	7	
Other	12	
Skin cancers		
Total	65 (74%)	198 (90%)
cSCC	61	185
MM	5	8
SGC	2	2
MCC subsets	1	1
cSCC only	57	
MM only	4	
MM + cSCC	1	
SGC + cSCC	2	
MCC + cSCC	1	
Metastatic cSCC	6	
Metastatic MM	3	

cSCC, cutaneous squamous cell carcinoma; MCC, Merkel cell carcinoma; MM, malignant melanoma; SGC, sebaceous gland carcinoma.

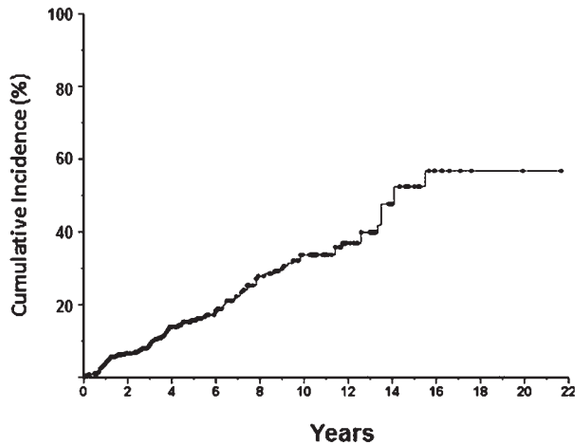

Figure 1 Cumulative incidence of second cancers in chronic lymphocytic leukaemia (CLL) patients. Data are shown as time from CLL diagnosis to first occurrence of any type of second cancer.

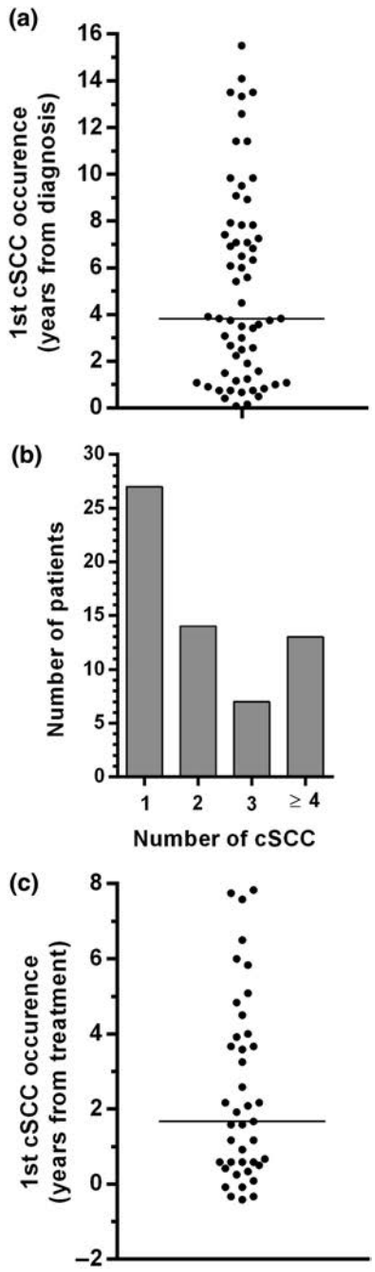

Figure 2 Timing and frequency of cutaneous squamous cell carcinoma (cSCC) occurrence. (a) The time from chronic lymphocytic leukaemia (CLL) diagnosis until the occurrence of the first cSCC is shown as a scatter plot with median time indicated by a horizontal line. (b) The number of patients presenting with one or multiple cSCC during follow-up is shown as a histogram. (c) The interval between occurrence of the first post-diagnosis cSCC and the start of treatment for CLL are shown as a scatter plot of cSCC date – treatment date with the solid line indicating the median time.

Incidence rates of cSCC were calculated and compared to those reported for the general NZ population (Fig. 3b, Table 3). Analysis was restricted to male CLL patients because of the low number of female CLL patients with cSCC. Incidence rates in the different age bands were 2.8–5.4-fold higher than those in the general population.

It is well established that some CLL patients have multiple cSCC, but the relative timing of these events is unclear[16] Therefore, the subgroup of patients who had ≥4 cSCC removed (n = 13) was analysed in more detail with respect to the temporal association between each occurrence of cSCC and the dates of significant clinical events, such as diagnosis, treatment for CLL and death (Fig. 4). These patients were all male and, although relatively young (median age = 61 years), had a median OS of only 6 years (data not shown). In all cases, once a second cSCC had occurred, all other recorded cSCC occurred, either at that same time or within a 3-year period. The majority of these patients (11/13) received treatment for CLL, and all cSCC occurred after or, in one patient, shortly before treatment. Of the 10 patients who died during follow-up, the first cSCC occurred within 5 years of diagnosis in all but the youngest patient. All subsequent cSCC and deaths in this group occurred within the following 5 years. A group of three patients with multiple cSCC, who had survived >12 years post-diagnosis, were all relatively young at diagnosis (age 47–61 years) and did not develop their second cSCC until after 10 years follow-up.

Full histological data were not available on all cSCC removed from these patients. However, in 11 of the 13 patients, there were sufficient data from at least one of their tumours to allow BWH staging; at least one cSCC staged as high risk (T stage 2b, 3) for 9 of these 11 patients.

Discussion

The high overall incidence of skin cancer in Australasia is well established. Despite reports that skin cancer incidence/aggressiveness is increased in CLL patients, little is known about the incidence of skin cancers, particularly cSCC, in Australasian CLL populations. In the present study, we report that the incidence of cSCC in a group of NZ CLL patients is significantly higher than that found in the general population and that almost all CLL patients who develop a cSCC will develop subsequent ones.

Ultraviolet radiation exposure and immunosuppression are both key risk factors for the development of skin

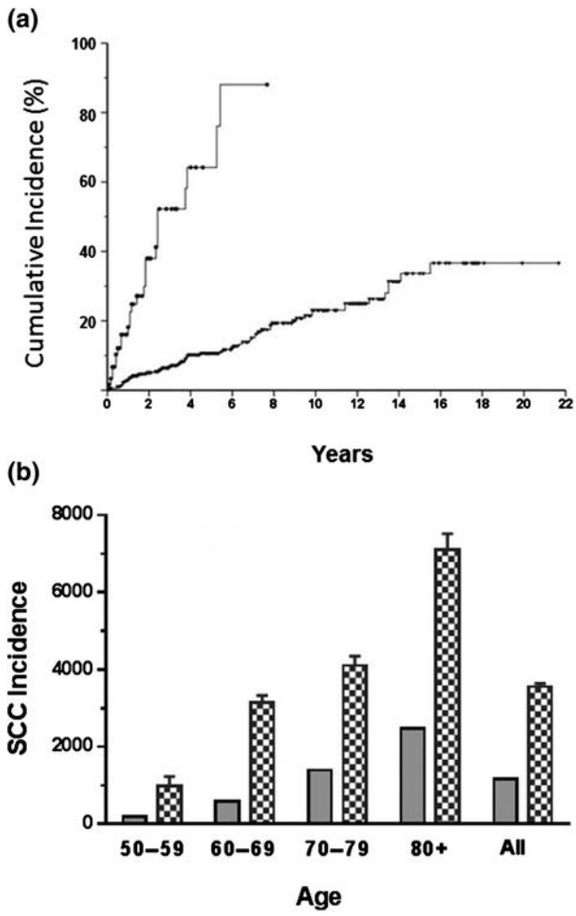

Figure 3 Incidence of cutaneous squamous cell carcinoma (cSCC). (a) The cumulative incidence of cSCC is shown as curves representing (i) time from chronic lymphocytic leukaemia (CLL) diagnosis to occurrence of first cSCC and (ii) time from occurrence of first cSCC to occurrence of a second cSCC. (●), Second cSCC; (▼), first cSCC. (b) Incidence of cSCC in males is shown as histograms representing cases per 100 000 person years for each age bracket. Only the first cSCC occurrence for each CLL patient was included in the analysis. Error bars indicate the 95% confidence interval for each rate. Data for a New Zealand (NZ) male population[26] were included for comparison. (▬), NZ population; (▩), CLL patients.

cancers. CLL is associated with a largely undefined, but profound, immunosuppression. This is thought to explain why CLL patients, similar to immunosuppressed transplant patients, have an increased incidence of aggressive skin cancers, particularly cSCC. In both Australia and NZ, there are relatively high levels of UV exposure. Consequently, the incidence of both MM and NMSC in the general population is substantially higher than that observed in the Northern Hemisphere.[9,26–28] Australian data have demonstrated that the high population rates of MM are

Table 3 Incidence of cutaneous squamous cell carcinoma (cSCC)†

	CLL patients			
Age	cSCC events	Person years	Incidence (95% CI)	NZ population Incidence
50–59	3	308	974 (835–1231)	181
60–69	16	508	3149 (3036–3332)	580
70–79	16	389	4113 (3964–4351)	1392
80+	16	225	7111 (6854–7522)	2468
All (50+)	51	1430	3566 (3512–3655)	1155

†NZ population data from Brougham *et al*.[26] Incidence calculated as first cSCC event per 100 000 person years. CI, confidence interval; CLL, chronic lymphocytic leukaemia; NZ, New Zealand.

even further increased in CLL patients.[9] This, together with Australasian data on cSCC occurrence in RTR,[21,22] suggest that the combination of high UV exposure and the immunosuppressed status of CLL patients will result in a high incidence of cSCC. The results of the current study confirm this, with incidences in the male CLL populations 2.8–5.4-fold higher than those of the general population, depending on the age bracket analysed. It is likely that the true figure is higher as only the first instance of cSCC was included in our analysis of CLL patients, and it is clear that CLL patients can have multiple cSCC within short periods of time. Studies using cancer registry data from countries

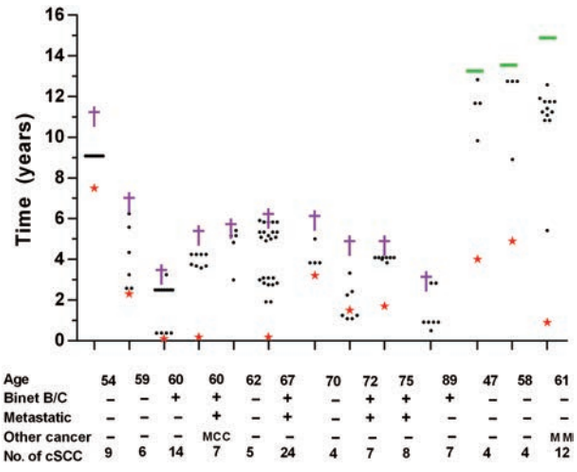

Figure 4 Features of patients with ≥4 cutaneous squamous cell carcinoma (cSCC). Data from patients who had ≥4 cSCC removed during follow-up are presented as a scatter plot. For each individual patient, the symbol (●) represents the time from chronic lymphocytic leukaemia (CLL) diagnosis until the occurrence of each cSCC. The time of death or censoring is shown as † or —, respectively, and the time of treatment for CLL as ★. Patient age and Binet stage at diagnosis, together with the number and metastatic state of occurring cSCC, are provided below the respective patient column. The other cancers specified were MM (malignant melanoma) and MCC (Merkel cell carcinoma).

like Finland, Sweden and Switzerland[12,13] have reported that male CLL patients have cSCC rates between 6-fold and 9.9-fold higher than expected. However, the background population rates of cSCC in those countries are up to 10 times lower than those in NZ.[26,28] This suggests that the overall incidence among NZ CLL patients is higher than reported in other countries. Further larger studies are required to confirm this. To date, only a single study has analysed the cumulative incidence of cSCC in CLL, and those results[7] closely resemble the results obtained in the current study (approximately 23% at 10 years). It is likely that the true incidence of NMSC is much higher than that reported as in many countries, including NZ, NMSC are not captured by cancer registries. In addition, cSCC removed by general practitioners without a matching histological record may contribute to data inaccuracy.

The possibility that the increased rate of cSCC in CLL merely reflects, at least in part, increased levels of skin surveillance cannot be fully addressed. However, there are no routine screening recommendations currently in place for CLL patients, making it unlikely this is a significant factor. In this regard, it is notable that a recent study at a US cancer centre reported low levels of compliance with skin cancer screening guidelines among CLL patients. Interestingly, in that study, the subgroup that underwent a full body skin examination within 6 months of CLL diagnosis had a high incidence of cSCC (15%).[29]

In the current study, the majority of patients in whom a cSCC occurred also received treatment for CLL during follow-up. Analysis of the relationship between first cSCC occurrence and treatment demonstrated that cSCC occurred predominantly either shortly before or within 2 years of treatment. Although this does not preclude treatment induction of cSCC, it suggests that cSCC occurrence is associated with the disease progression that necessitates treatment.

A feature of NMSC incidence in immunosuppressed transplant patients is the frequent occurrence of multiple NMSC.[22] Data from CLL patients have clearly demonstrated that multiple cSCC occur in at least some patients. However, the proportion of patients and the time between first and subsequent cSCC have not been previously reported. In the current study, analysis of cumulative incidence indicates that almost all CLL patients who develop a cSCC will develop a subsequent cSCC within 5 years, with a median time between the first and second cSCC of 29 months. This time interval is similar to the 26 months reported for RTR at the same hospital[22] and supports the concept that immunosuppression plays an important role in cSCC occurrence in both types of patients. This study did not specifically analyse the contribution of cSCC recurrence to the increased incidence of subsequent cSCC. However, an Australian study of 42 patients who presented with primary cSCC reported elevated rates of subsequent local recurrence and nodal disease.[18] This, together with other studies, suggests that cSCC in the context of CLL are often multiple, with a tendency for local and regional recurrence.[7,17]

It has been reported that mortality specifically because of the occurrence of the skin cancers MM and MCC is significantly higher in CLL patients.[14] Numerous studies have reported that the cSCC in CLL patients are associated with increased rates of recurrence, metastasis and cSCC-specific mortality. This is consistent with anecdotal reports that the occurrence of multiple cSCC is associated with poor clinical outcomes. However, to date, only a single study has analysed the contribution cSCC makes to the overall mortality of CLL patients. In that study of CLL patients with skin cancers, of which almost all were cSCC, the mortality was as high from skin cancer as from CLL.[16] The predictors of poor outcomes had a high Rai stage at diagnosis, the occurrence of multiple cSCC (>5) and occurrence of tumours with a high T stage. This is consistent with the general features of those patients in our study who had ≥4 cSCC during follow-up; the majority had at least one cSCC with a high T stage and died within 7 years of diagnosis. The temporal association of treatment, cSCC occurrence and death in CLL patients with skin cancer has not been previously reported. A general pattern of events was apparent in these patients; the first cSCC often appeared early following diagnosis, and once a second cSCC had occurred, the remaining cSCC and death occurred within 5 years. The cause of death in these patients is not known. This, together with the small number of patients analysed, precludes any assessment of whether the occurrence of multiple cSCC makes any contribution to the mortality of these patients. These observational results do, however, provide a useful illustration of the general pattern of multiple cSCC occurrence in relation to the timing of other clinical events. This emphasises the need for effective screening once a cSCC has occurred and supports further studies to evaluate the usefulness of skin cancer staging in risk stratification of CLL patients

In the interpretation of our results, a number of limitations must be considered, including the retrospective nature of the analysis, and the relatively small number of patients involved. The limited information regarding prognostic markers and additional outcome measures, such as cSCC-related mortality, make it possible to draw only broad conclusions. However, despite these caveats, this study provides useful information about real-life outcomes in a community-based hospital population.

Conclusion

New Zealand CLL patients have a high incidence of cSCC relative to the levels observed in the general population, which are themselves among the highest in the world. Therefore, close surveillance and prompt treatment of skin cancer occurrence in CLL patients is warranted, particularly for those who have progressive disease or have previously had cSCC.

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Outcomes and predictors of response from an optimised, multidisciplinary intervention for chronic fatigue states

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Key words
chronic fatigue syndrome, post-cancer fatigue, exercise therapy, cognitive behaviour therapy.

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Abstract

Background: Medically unexplained chronic fatigue states are prevalent and challenging to manage. Cognitive behavioural therapy (CBT) and graded exercise therapy (GET) are effective in clinical trials. The evaluation of delivery in a standard healthcare setting is rare. An integrated treatment programme with individualised allocation of resources to patients' needs was developed and implemented through an academic outpatient clinic. It was hypothesised that the programme would result in similar responses to those observed in the clinical trials.
Aim: To evaluate the outcomes of an integrated, 12-week CBT and GET programme delivered by exercise physiologists and clinical psychologists.
Methods: Consecutive eligible patients (n = 264) who met the diagnostic criteria for chronic fatigue syndrome or post-cancer fatigue were evaluated with self-report measures of fatigue, functional capacity and mood disturbance at baseline, end-of-treatment (12 weeks) and follow-up (24 weeks). A semi-structured interview recording the same parameters was conducted pre- and post-treatment by an independent clinician. Primary outcome was analysed by repeated measures analysis of variance and predictors of response were analysed by logistic regression.
Results: The intervention produced sustained improvements in symptom severity and functional capacity. A substantial minority of patients (35%) gained significant improvement, with male gender and higher pain scores at baseline predicting non-response. A small minority of patients (3%) worsened.
Conclusion: The manualised protocol of integrated CBT and GET was successfully implemented, confirming the generally positive findings of clinical trials. Assessment and treatment protocols are available for dissemination to allow standardised management. The beneficial effects described here provide the basis for ongoing studies to optimise the intervention further and better identify those most likely to respond.

Introduction

Fatigue is a common symptom of many illnesses in primary care, ranging from minor infection to major depression.[1] A small subset of such patients experience persistent and severe fatigue accompanied by musculoskeletal pain and neurocognitive difficulties as well as sleep and mood disturbances.[1] This chronic fatigue state

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is considered 'unexplained' when history, examination and laboratory investigation does not reveal a medical or psychiatric diagnosis. Such medically unexplained fatigue syndromes include chronic fatigue syndrome (CFS)[2] and post-cancer fatigue (PCF),[3] which share core symptoms.[4] The prevalence of CFS is between 0.2 and 2.6% worldwide,[5] and it is recognised that 11% of patients surviving cancer will suffer PCF lasting 6 months or more.[6] Such syndromes are associated with significant disability, healthcare utilisation and economic impact.[5,7]

Despite sustained research efforts, the pathophysiology of these medically unexplained fatigue states remains obscure.[5,7] Although many randomised controlled trials of a broad array of pharmacological agents have been conducted, there is currently no evidence-based curative therapy.[5,7] Accordingly, the current treatment goals are to reduce symptom severity and improve functional status. With these goals in mind, there is independently replicated randomised control trial evidence for graded exercise therapy (GET) and cognitive behavioural therapy (CBT) in CFS and growing evidence in PCF.[7,8] These treatments achieve positive outcomes by first managing the common comorbidities, which worsen symptoms and impair function, including disrupted sleep, depression and anxiety. In addition, the intervention seeks to improve management of excessive, or avoidant, activity patterns by activity pacing, and to facilitate graduated increases in physical activity. Although the results are generally positive, the reported CBT and GET interventions vary significantly in the details of the intervention, with evidence also available for the significant effects of the study site and individual therapist on outcomes.[7–9] Additionally, it is frequently the case that studies of CBT have included aspects of GET intervention and vice versa. In fact, the only study that explicitly sought to isolate these interventions (the 'Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy and specialist medical care for chronic fatigue syndrome' (PACE) trial)[10] reported improvements and similar effect sizes after both CBT and GET, and a mediation analysis suggested that benefit was primarily through the reduction of fear avoidance of activity.[11] Evaluations of outcomes in community-based studies have focused solely on CBT, but incorporate unstructured elements of GET rather than formalising the two.[12–14] Accordingly, an outpatient, integrated CBT and GET treatment programme was established within an academic research framework at the Lifestyle Clinic, University of New South Wales.

The goals of the programme were to utilise standardised instruments and protocols for patient assessment, apply individualised interventions from structured treatment modules and assess the effectiveness and predictors of outcome.

In contrast to previous studies, the programme described here provides treatment elements (CBT components, activity pacing, graded exercise) in an integrated fashion, with individualised allocation of resources to the patients' needs. It was hypothesised that the practical implementation of a modularised integrated CBT and GET programme would result in similar improvements to published randomised control trials.

Methods

Patient selection

Between 2008 and 2013, consecutive patients were enrolled from those referred by general practitioners to the Fatigue Clinic at the Lifestyle Clinic, University of New South Wales, which is a multidisciplinary outpatient treatment service that is staffed by accredited exercise physiologists and clinical psychologists and led by an academic physician (Fig. 1). Patients were referred under public sector, government-subsidised mechanisms. Patients were eligible if they had a specialist physician diagnosis of a chronic fatigue state (i.e. either CFS or PCF) meeting international diagnostic criteria for the relevant condition,[2,3] attended at least one appointment, completed baseline questionnaires and reported 'clinically significant' fatigue (on the Somatic and Psychological Health Report (SPHeRe) questionnaire – see below) and provided written informed consent for their data to be used in the analysis. The study was approved by the Human Research Ethics Committee of the University of New South Wales.

Study design and intervention

A manualised, 12-week, multidisciplinary outpatient treatment programme, including five individual 1-h consultations with an exercise physiologist and six to eight individual 1-h consultations with a clinical psychologist were conducted approximately fortnightly. The programme included two integrated treatment arms (see Fig. 1 and Table 1 for further intervention details) (treatment protocols and resources are available on request). The first comprised compulsory modules focused on activity pacing and GET delivered by an exercise physiologist. The activity pacing component was based on the 'envelope' theory of CFS,[15] which suggests that the disorder is associated with a limited energy supply, with exacerbations of fatigue triggered by 'excessive' activity resulting in prolonged inactive periods. The activity pacing intervention encouraged patients to avoid exacerbations by planning daily and weekly schedules of activities and rest breaks and segmenting tasks into short

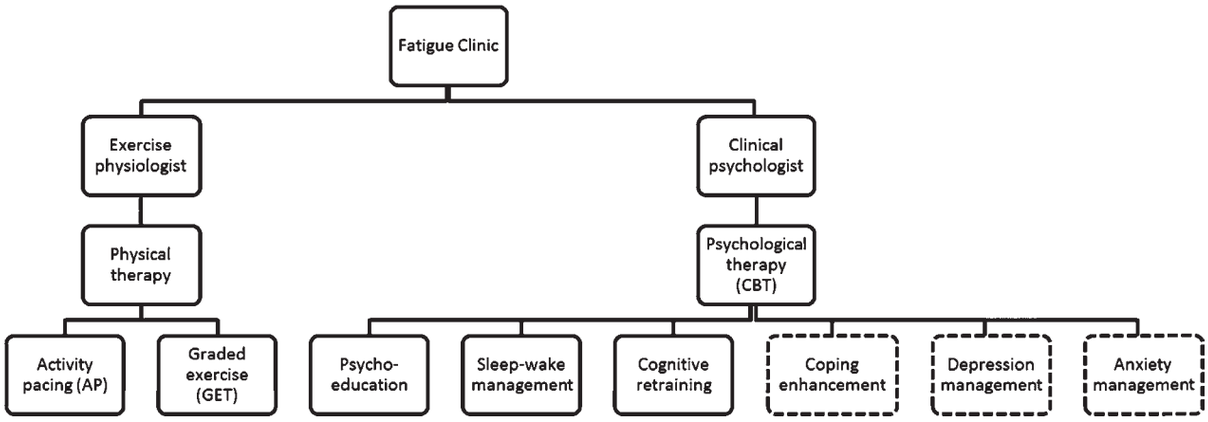

Figure 1 Overview of the Fatigue Clinic programme, including the two integrated treatment arms and the individual treatment modules. The first arm comprised modules focused on activity pacing (AP) and graded exercise therapy (GET), which were delivered by an exercise physiologist. The second arm comprised three compulsory modules delivered in a typical cognitive behavioural therapy (CBT) framework by a clinical psychologist: psycho-education, sleep–wake cycle disturbance management and neurocognitive disturbance management. In addition, three optional modules (dashed line) were applied to patients with significant depression, anxiety or poor coping.

time blocks. In contrast to adaptive pacing of the PACE trial, activity pacing was used as a precursor to GET. The GET component was based on the notion of central sensitisation to physiological signals and hence desensitisation (i.e. carefully graduated exposure to the triggering stimuli – exercise) to reduce the exaggerated (brain-derived) symptom of fatigue.[16] Accordingly, the GET intervention established an initial achievable level of structured regular exercise (e.g. walking), in addition to activities of daily living, followed by graduated increases in exercise duration by approximately 20% of the nominated duration every 2–3 weeks, generally at a fixed low intensity. Once 30 min of continuous activity was achieved, the frequency of exercise sessions was increased. Daily step counts were recorded through pedometry for monitoring and feedback to ensure patients were maintaining agreed levels of activity.

The second arm comprised three compulsory modules provided in a typical CBT framework as developed for CFS and PCF[17,18] and delivered by a clinical psychologist: psycho-education[19] about the illness and the rationale for intervention; sleep–wake cycle disturbance management,[19] which sought to optimise sleep hygiene, notably to minimise daytime napping and to ensure an

Table 1 Outline of the combined CBT and GET intervention

	Clinical psychologist	Exercise physiologist
Week 1	Psychological assessment and introduction to programme – clinical interview	Assessment and introduction to programme – clinical interview Sleep, symptom and activity diaries provided Pedometer provided
Week 3	Introduction to CBT Psycho-education for sleep Introduction to cognitive activity pacing	Review diary Implement activity pacing Provide step count diary
Week 5	Address barriers to pacing Address, mood, coping, sleep or anxiety	Review activity pacing Introduce GET
Week 7	Review mood, coping sleep or anxiety Introduce CET	
Week 9	Address barriers to pacing and/or CET Review mood, coping, sleep or anxiety Review CET progress	Address barriers to pacing and/or GET Review GET progress
Week 12	Review progress and long-term CET plan Goal setting for the post-intervention period	Review progress and long-term GET plan Goal setting for the post-intervention period

An additional two sessions were offered to selected patients who required further support. CBT, cognitive behavioural therapy; CET, cognitive exercise therapy; GET, graded exercise therapy.

unbroken, regimented night-time sleep routine and neurocognitive disturbance management,[20] essentially a cognitive remediation approach analogous to GET. In addition, three optional modules of problem-focused CBT were applied to patients with significant clinician-designated depression, anxiety or poor coping.[17,19]

Appointments were scheduled consecutively with the two clinicians, allowing a handover to ensure a consistent management plan. Additionally, monthly clinical review meetings were conducted with the physician. If it became apparent that management-limiting comorbid conditions were evident, such as uncontrolled pain or depressive disorder, the patient was referred back to their general practitioner or specialist to ensure that these issues were optimally managed before returning to the programme in order to ensure maximal benefit from the fatigue-focused intervention.

Assessment

The initial assessment included clinical interviews with each practitioner and self-report questionnaires (see following) assessing the presence and severity of fatigue, pain, physical functional capacity and disturbances in sleep and mood. Following the first appointment, patients also completed a detailed daily diary, recording symptoms, activities and sleep patterns for 10–14 days. In combination, these parameters allowed the clinicians individually to prioritise treatment modules. For example, this approach allowed greater focus on the management of anxiety disorders or sleep–wake cycle disorders in some patients and on activity pacing and GET where these problems were not significant.

Outcome measures

At baseline, end-of-treatment (12 weeks) and follow-up (24 weeks), the following self-report questionnaires were administered: the SPHeRe,[21] which is a 34-item instrument assessing a range of somatic and psychological symptoms commonly used in the assessment of patients with CFS and PCF.[22] The SPHeRe includes two 6-item subscales that have been validated to designate 'clinically significant' fatigue (somatic (SOMO)), with a score of 3 or more (possible range 0–12, 12 = worst),[23] and mood disorder, with a score of 2 or more (possible range 0–12, 12 = worst).[21,24] The primary outcome measure was a statistically significant improvement in fatigue (SOMA) at end-of-treatment and follow-up.

The Pittsburgh Sleep Quality Index[25] was utilised to assess sleep pattern and quality (possible range 0–21, 21 = worst). The McGill Pain Questionnaire was used to record musculoskeletal pain.[26,27] The RAND 36-item Short-Form Health Survey (SF-36)[28,29] was used to measure functional status, notably the physical function and social functioning subscales (possible range 0–100, 100 = best). An independent psychologist conducted the Semi-structured Clinical Interview for Neurasthenia (SCIN)[30] on a subset of patients at baseline and follow-up to validate self-reported outcomes. Using these instruments, the secondary outcomes included statically significant improvements in functional outcomes, mood and sleep.

Statistical analyses

Data were analysed using the Statistical Package for Social Sciences (SPSS v19; SPSS, Armonk, NY, USA) for all eligible patients by intention-to-treat (ITT) where missing data were carried forward from earlier results and also for those with complete datasets (CD) across all three time points. Chi-square tests were conducted to compare categorical variables and unpaired two-tailed *t*-tests for continuous variables. These test were used to compare demographic and baseline illness variables between CD and ITT datasets and between CFS and PCF participants. The primary outcome was analysed by one-way repeated measures analysis of variance with Bonferroni post hoc tests. Correlations between self-reported and clinician-assessed outcomes were sought using Spearman's statistic. For the analysis of the predictors of outcome by logistic regression, the sample was categorised into treatment 'responders' and 'non-responders', where treatment response was designated a priori as improvement in scores equivalent to at least one standard deviation (SD) of the variance in fatigue (SOMA) across the patient group at baseline. In addition, the comparable criterion of 0.5 SD, as utilised in the PACE trial,[10] was applied to allow comparison. Logistic regression was used to identify variables potentially associated with treatment response based on previous literature, including age, gender, duration of illness, pain, sleep and mood disturbances.[31] Effect size (Cohen's *d*) was also calculated.[32] Alpha was set at $P < 0.05$ with 95% confidence intervals (CI).

Results

Participants

Of the 389 patients who attended the clinic, 264 (68%) met the eligibility criteria for inclusion. The reasons for non-inclusion ($n = 125$, 32%; see Fig. 2) included the lack of a specialist-confirmed diagnosis, alternative diagnoses ($n = 20$; 16%) and fatigue scores below the threshold. The CD group comprised 168 patients (64%).

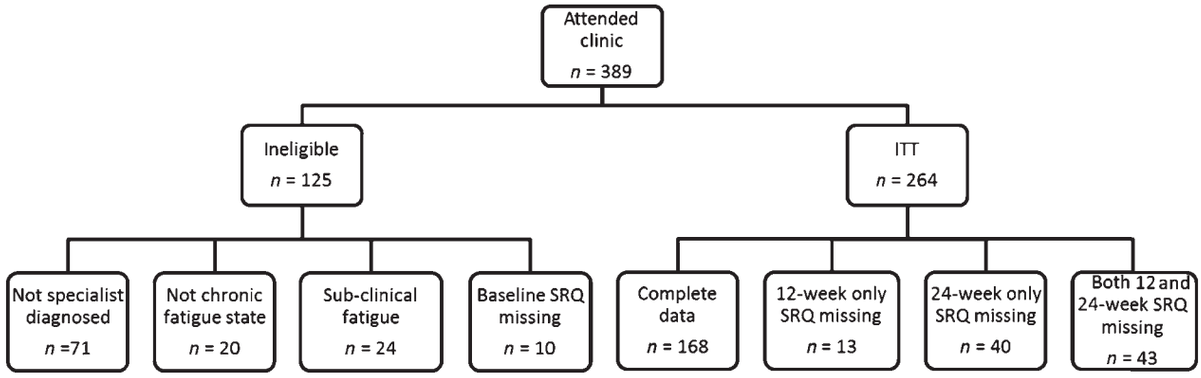

Figure 2 Consolidated Standards of Reporting Trials (CONSORT) diagram. SRQ, self-report questionnaire.

The patients were predominantly female (177 of 264; 67%), and most had been diagnosed with CFS (93% of ITT group and 93% of CD group). They had been suffering from chronic fatigue for a mean (*M*) of 4.9 years, with a substantial minority receiving Sickness Benefits or a Disability Support Pension (n = 104; 39%) (Table 2). Patients with CFS reported significantly greater fatigue at baseline (M = 8.4, SD = 2.7) compared to those with PCF (M = 6.6, SD = 2.3; t (262) = −2.9, $P < 0.01$), had a longer sickness duration (M = 5.0 years, SD = 3.6 vs M = 3.1, SD = 3.4; t (261) = −2.201, $P < 0.05$) and were younger (M = 36 years, SD = 13.3 vs M = 48, SD = 11.3; t (22) = 4.5, $P < 0.01$).

Table 2 Demographic and illness characteristics of the patients with chronic fatigue states

	CD (n = 168)	ITT (n = 264)	*P*
Mean age, years (SD)	36.8 (14)	36.7 (14)	0.88
Diagnosis, number with CFS (%)	157 (93)	245 (93)	0.77
Gender, number of female (%)	107 (64)	177 (67)	0.16
Education, number greater than 10 years (%)	149 (89)	233 (88)	0.97
Married/de facto, *n* (%)	69 (41)	108 (41)	1.00
Mean duration of illness, years (SD)	4.6 (3.7)	4.9 (3.7)	0.13
Sickness benefits/pension, *n* (%)	68 (0)	104 (39)	0.65
Mean fatigue score – SOMA (SD)	8.3 (2.8)	8.3 (2.7)	0.63
Mean physical function score – SF-36 (SD)	46.8 (21.5)	46.68 (22.2)	0.95
Presence of mood disturbance, *n* (%)	120 (71.4)	198 (75)	0.67
Mean social functioning score – SF-36 (SD)	32.1 (22.0)	31.5 (22.3)	0.71
Mean global sleep score – PSQI (SD)	9.2 (3.7)	9.3 (3.8)	0.62

CD, complete data analysis; CFS, chronic fatigue syndrome; ITT, intention-to-treat analysis; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; SF-36, Medical Outcomes Study Short-Form 36-item; SOMA, somatic.

Treatment outcomes

Fatigue and physical function

The severity of self-reported fatigue improved significantly between baseline and end-of-treatment at 12 weeks (M_{diff} = −1.82, 95% CI: −2.23 to 1.4, $P < 0.001$) and between baseline and follow-up at 24 weeks (M_{diff} = −1.42, 95% CI: −1.84 to −1.00, $P < 0.001$) (Fig. 3). This improvement was generally sustained, albeit with some deterioration from end-of-treatment to follow-up (M_{diff} =0.39, 95% CI: 0.04–0.74, $P < 0.05$). There were consistent improvements in physical function (SF-36) between baseline and end-of-treatment (M_{diff} = 2.35, 95% CI: 0.18–4.53, $P < 0.05$) and end-of-treatment to follow-up (M_{diff} = 2.26, 95% CI: 0.18–4.33, $P < 0.05$). These results translate to an effect size of d = 0.60. The findings were similar in the CD group. A subgroup analysis of participants with a diagnosis of CFS alone was conducted, which showed no difference in the primary outcome (F (2, 243) = 51.09, $P < 0.001$).

These self-reported improvements in fatigue and functional status were mirrored in the subgroup with interviewer-designated outcomes through the SCIN (n = 44), with significant decreases in fatigue scores from baseline (M = 11.66, SD = 2.69) to post-treatment (M = 8.82, SD = 4.07, t (43) = 3.98, $P < 0.01$; 95% CI: 1.40–4.28). There was a positive correlation between the self-report and clinician-designated fatigue scores at baseline (r = 0.39, n = 44, $P < 0.05$) and follow-up time points (r = 0.45, n = 44, $P < 0.01$).

Mood and social function

The levels of mood disturbance also decreased significantly between baseline and end-of-treatment (M_{diff} = −1.18, 95% CI: −1.64 to −0.72, $P < 0.001$) and follow-up (M_{diff} = −1.06, 95% CI: −1.49 to −0.62, $P < 0.001$) (Fig. 4). No additional improvement between end-of-

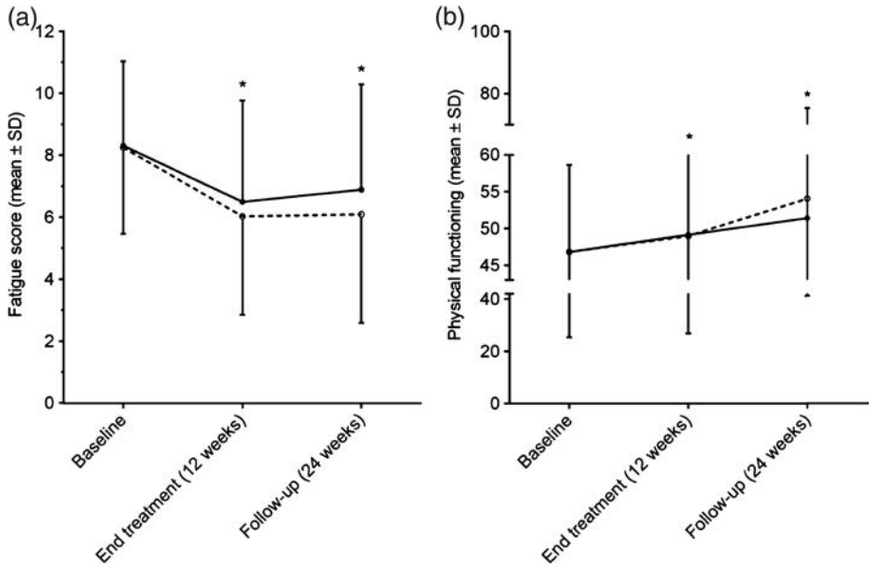

Figure 3 Changes in fatigue severity (a) and physical function (b) during and after treatment. Mean and standard deviation (SD) are shown for the intention-to-treat analysis (ITT) and complete data analysis (CD) analysis at each time point. The fatigue severity score was obtained from the Somatic subscale of the Somatic and Psychological Health Report questionnaire and physical functioning from the Physical Functioning subscale of the Medical Outcomes Study Short-Form 36 (SF-36) questionnaire. Asterisks (*) represent differences from baseline in reference to the ITT analysis. (—•—), ITT $F(2, 262) = 58.03$, $P < 0.001$; (-•-), CD $F(2, 166) = 50.43$, $P < 0.001$.

treatment and follow-up was seen ($M_{diff} = -0.13$, 95% CI: −0.50 to 0.25, $P = 1.00$). The improvement in mood was associated with enhanced social functioning (Fig. 4) at end-of-treatment ($M_{diff} = 6.30$, 95% CI: 2.77–9.82, $P < 0.001$) and follow-up ($M_{diff} = 6.97$, 95% CI: 3.75–10.18, $P < 0.001$). There was no further increase in social functioning from end-of-treatment to follow-up ($M_{diff} = -0.67$, 95% CI: −2.58 to 3.92, $P = 1.00$). A comparable trend was observed in the CD analysis.

These self-reported benefits were confirmed through the clinician assessments through the SCIN, which improved from baseline ($M = 3.41$, SD = 1.99) to post-treatment ($M = 2.59$, SD = 2.07; t (43) = 4.55, $P < 0.01$; CI: 0.26–1.37). There was a strong correlation between self-reported and interviewer-designated mood disturbance scores at both pretreatment ($r = 0.53$, $n = 44$, $P < 0.01$) and follow-up time points ($r = 0.59$, $n = 44$, $P < 0.01$).

Treatment response and predictors

Just over one third of patients ($n = 91$, 35%) gained more than one SD of improvement at end-of-treatment (Table 3). This improvement was generally sustained at follow-up ($n = 78$, 30%). A more liberal designation of

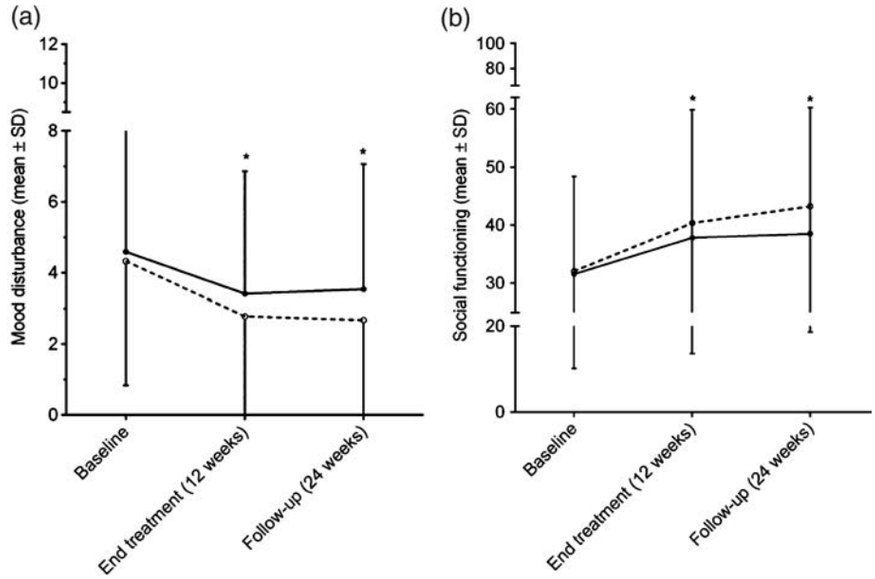

Figure 4 Changes in mood (a) and social function (b) during and after treatment. Mean and standard deviation (SD) are shown for the intention-to-treat analysis (ITT) and complete data analysis (CD) analyses at each time point. The mood disturbance score was obtained from the Psychological subscale of the Somatic and Psychological Health Report questionnaire and social function from the Social Functioning subscale of the Medical Outcomes Study Short-Form 36 (SF-36) questionnaire. Asterisks (*) represent differences from baseline in reference to the ITT analysis. (a) (—•—), ITT $F(2, 257) = 22.06$, $P < 0.001$; (-•-), CD $F(2, 12) = 22.08$, $P < 0.001$. (b) (—•—), ITT $F(2, 260) = 15.14$, $P < 0.001$; (-•-), CD $F(2, 166) = 16.99$, $P < 0.001$.

Table 3 Response rates to treatment with cognitive behavioural therapy and graded exercise therapy

	End-of-treatment 12 weeks	Follow-up 24 weeks
1 SD improvement in fatigue score, *n* (%)	91 (34.5)	78 (29.5)
0.5 SD improvement in fatigue score, *n* (%)	126 (47.7)	102 (38.6)
1 SD deterioration, *n* (%)	7 (2.7)	13 (4.9)

SD, standard deviation.

response (0.5 SD) indicated that 126 patients (48%) gained improvement at end-of-treatment. Patients classified as treatment responders (>1 SD) showed improvement in physical function scores, from a mean of 49.4 at baseline to 57.6 at end-of-treatment and 58.8 at follow-up. This measure of improved physical function typically implied a change in the capacity to 'walk more than 2 kilometres' from 'limited a lot' to 'limited a little' (n = 13) or from 'limited a little' to 'not limited at all' (n = 12).

The analysis for predictors of treatment response was significant at end-of-treatment (χ^2 (7, n = 246) = 21.83, $P < 0.01$). Female gender and lower pain scores at baseline were independently associated with the response (Table 4).

Adverse effects

An increase in the fatigue score of 1 SD from the baseline was designated as a significant adverse outcome. There were seven patients (3%) who met this criterion (Table 3), of whom only one did not complete treatment. The remaining six had emergent psychiatric or medical comorbidities, notably depression and pain (individual data not shown).

Discussion

This 'real-world' application of the only evidence-based intervention for chronic fatigue states confirms the findings of clinical trials. There were significant reductions in the severity of fatigue and comorbid mood disturbance, accompanied by improvements in functional status. Just over one third of patients experienced a clinically significant improvement in fatigue after treatment, and this was generally sustained 3 months following treatment. Additionally, the positive outcomes were corroborated through the SCIN, which allows a more robust evaluation of fatigue and accompanying symptoms. In conjunction with published literature, these data suggest that an integrated multi-modal treatment approach should be made widely available to patients with chronic fatigue states. This is the first protocol-driven, integrated CBT and GET intervention evaluation in a public sector health service. The study presented here used standardised pretreatment assessments to inform application of the individual treatment modules, followed by standardised monitoring tools to ensure optimal ongoing application of the intervention.

A previously conducted evaluation of six UK National Health Service clinical services that provide specialist care for patients with CFS showed variation in the delivery of treatment (e.g. group as well as individualised sessions).[12] Additionally, CBT and GET were delivered in isolation for some patients, but in combination for others. The study presented here used standardised pretreatment assessment to inform application of the eight individual treatment modules followed by standardised monitoring tools to ensure optimal ongoing application of the intervention.

Significant improvements in the severity of fatigue and associated physical functional capacity were evident at the end-of-treatment and at follow-up 3 months later. This is in line with the treatment protocol that aimed first to stabilise day-to-day and week-to-week fluctuations in symptoms through activity pacing before embarking upon concerted efforts to increase function through GET. The pre-post effect size of 0.60 in this study is comparable to previously reported effects sizes of 0.41 for GET and 0.36 for CBT in individual meta-

Table 4 Predictors of response to cognitive behavioural therapy and graded exercise therapy treatment

Variables	End-of-treatment 12 weeks			Follow-up 24 weeks		
	P	Odds ratio	95% CI	*P*	Odds ratio	95% CI
Age	0.70	1.00	(0.78–1.02)	0.32	0.99	(0.97–1.01)
Gender	<0.05*	0.53	(0.28–0.99)	0.14	0.62	(0.33–1.17)
Duration of illness	0.07	1.00	(1.00–1.00)	0.12	1.00	(1.00–1.00)
Pain	<0.01*	0.91	(0.86–0.97)	0.23	0.96	(0.91–1.02)
Sleep disturbance	0.16	1.06	(0.98–1.14)	0.47	1.03	(0.95–1.11)
Mood disturbance	0.42	1.03	(0.96–1.12)	0.43	0.97	(0.89–1.05)
Physical functioning	0.44	1.01	(0.99–1.02)	0.25	1.01	(0.99–1.02)

*Statistical significance at $P < 0.05$. CI, confidence interval.

analyses,[8] although it should be noted that these values were compared to control conditions. In the largest controlled trial of CBT and GET reported to date, the PACE trial, which evaluated activity pacing, GET and CBT individually versus specialist medical care in the UK,[10] the criterion for a response was set liberally at 0.5 SD. This study showed that over the 52-week intervention, only CBT and GET were superior to specialist medical care, with response rates of 76% for CBT and 80% for GET, compared with 48% in the present study. In addition to being outside a clinical trial context, patients in the current report received a shorter intervention and had a longer illness duration than those in the UK study. The magnitude of improvements in mental health and associated social functioning reported here was consistent with other real-world studies that have sought to reduce comorbid mood disturbances in patients with CFS.[12]

Concurrent pain was the major predictor of non-response to treatment, consistent with previous studies.[33] Uncontrolled pain is likely to impede treatment success by reducing activity pacing, disturbing sleep, lowering mood and especially by restricting GET.[34] This argues for a sequential approach in patients with concurrent pain, with an initial focus on physical, pharmacological and psychological approaches to pain management analogous to the recommendations for fibromyalgia,[35] followed by the fatigue-focused CBT and GET intervention. It is also noteworthy that the duration of illness did not influence treatment response in the data reported here, consistent with findings in the PACE trial and other reports.[10]

Study limitations

The limitations of this study include delivery of the intervention in an outpatient setting, necessitating attendance for up to 2 h per fortnight over a 3-month period, which would not be feasible for the small subset of severely affected patients. In addition, in both CFS and PCF, some patients were predominantly disabled by neurocognitive difficulties, such as impairments in concentration and short-term memory. The intervention described here included some cognitive remediation, but symptom scores in this domain (data not shown) remained elevated in the face of improvement in fatigue, arguing for the need of a targeted neurocognitive intervention. Finally, in the absence of a randomly allocated control group receiving standard medical care, it is not possible to interpret the outcomes from this study relative to likely changes without access to a combined CBT and GET intervention.

Conclusion

The findings from this multidisciplinary outpatient treatment programme for chronic fatigue states argue for integrated GET and CBT as an effective treatment. Further studies seeking to enhance the magnitude of symptomatic and functional benefit and also to increase the proportion of those responding to therapy are warranted, potentially followed by the development of healthcare models to allow widespread delivery, perhaps by web-based or telephone methods.

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Effect of a general practitioner management plan on health outcomes and hospitalisations in older patients with diabetes

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Key words
diabetes, care plan, general practice, hospitalisation.

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Abstract

Background: Little is known about the impact of a general practitioner management plan (GPMP) on health outcomes of patients with diabetes.
Aim: To examine the impact of a GPMP on the risk of hospitalisation for diabetes.
Methods: A retrospective study using administrative data from the Australian Government Department of Veterans' Affairs was conducted (1 July 2006 to 30 June 2014) of diabetes patients either exposed or unexposed to a GPMP. The primary end-point was the risk of first hospitalisation for a diabetes-related complication and was assessed using Cox proportional hazard regression models with death as a competing risk. Secondary end-points included rates of receiving guideline care for diabetes, with differences assessed using Poisson regression analyses.
Results: A total of 16 214 patients with diabetes were included; 8091 had a GPMP, and 8123 did not. After 1 year, 545 (6.7%) patients with a GPMP and 634 (7.8%) of patients without a GPMP were hospitalised for a diabetes complication. There was a 22% reduction in the risk of being hospitalised for a diabetes complication (adjusted hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.69–0.87, $P < 0.0001$) for those who received a GPMP by comparison to those who did not. Increased rates of diabetes guideline care, HbA1c claims (adjusted HR 1.29, 95% CI 1.25–1.33) and microalbuminura claims (adjusted HR 1.65, 95% CI 1.58–1.72) were observed after a GPMP.
Conclusion: Provision of a GPMP in older patients with diabetes resulted in improved health outcomes, delaying the risk of hospitalisation at 12 months for diabetes complications. GPMP should be included as part of routine primary care for older patients with diabetes.

Introduction

The prevalence of diabetes continues to increase worldwide, with estimates that if the current epidemic is not addressed and trends continue, as many as one in three people in the United States could have diabetes by 2050.[1] The total estimated cost of diagnosed diabetes in 2012 in the United States was $245 billion, which included $176 billion in direct medical costs. In Australia, approximately one million people were diagnosed with diabetes in 2012, with more than 10 000 new cases diagnosed each year, with an annual care cost of $A14.6 billion dollars.[2,3] Hospital inpatient care is the largest component of medical expenditure for people with diabetes, accounting for 43% of the total medical costs.[4] In many cases, hospitalisation for diabetes-related complications may be avoided with high-quality primary and preventive care.[5]

Multidisciplinary models of care have been shown to be effective in improving diabetes care and health outcomes in patients with diabetes.[6,7] The Australian government funded the Chronic Disease Management programme to encourage improved and coordinated multidisciplinary care for patients with chronic

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conditions and complex care needs. The programme provides fees for a GP-initiated care plan, known as a general practitioner management plan (GPMP). In patients with diabetes, this national chronic disease management programme has led to improvements in recommended care practices, including measurement of glycated haemoglobin (HbA1c) and access to allied health services.[8,9] Our previous study showed that over a third of older people with diabetes had received a GPMP between 2006 and 2008, a significantly higher rate compared to people with other chronic conditions.[10] No research to date has examined the impact of a GPMP on long-term health outcomes of people with diabetes. The primary aim of this study was to examine the impact of a GPMP on the risk of hospitalisation for diabetes complications in older people with diabetes. A secondary aim was to examine the effect of a GPMP on the rate of guideline-recommended care practices for people with diabetes.

Methods

This study was approved by the Australian Government Department of Veterans' Affairs (DVA) and the University of South Australia Human Research Ethics Committees.

Data source and study design

A retrospective cohort study was undertaken between 1 July 2006 and 30 June 2014 using administrative health data from the DVA claims database. The DVA claims database contains details of all prescription medicines, medical, allied health services and hospitalisations subsidised by DVA for a treatment population of 240 000 veterans, war widows and widowers. Over 70% of the population are aged 70 years or older; 54% are male, and 9.8% live in residential aged care.[11] In the dataset, medicines are coded according to the Anatomic, Therapeutic and Chemical Classification[12] and the Pharmaceutical Benefits Schedule.[13] Medicare services are coded according to the Medicare Benefits Schedule (MBS).[14] Hospitalisations are coded according to the International Classification of Diseases, version 10, -Australian modification (ICD-10-AM).[15]

The study included all subjects aged 65 years and over with diabetes, eligible for all health services subsidised by DVA, who were living in the community during the study period (exclusion of subjects in residential care). Diabetes was defined by at least two dispensings of an anti-diabetic medicine in the year prior to study entry. The exposed group included patients who had had a GPMP (MBS item 721) during the study period between 1 July 2008 and 30 June 2014. The unexposed group included patients who had not had a GPMP or claims for items related to care plans (MBS 720–732) during the study period or the 2 years prior (1 July 2006 to 30 June 2008). The eligibility of the veterans for the unexposed group was determined on a monthly basis throughout the study period. Eligible unexposed patients were randomly allocated to an index month in the study period to match the time of the GPMP in the exposed group. They were matched only once in the study period. The date of the GPMP for the exposed group or the matched time in the unexposed group was the study entry.

The primary end-point was the risk of hospitalisation for a diabetes-related complication in the 12 months following study entry (defined as time of GPMP in exposed group and matched index month in the unexposed group). This was defined by hospitalisation (ICD-10AM codes E10-E14) as a principal diagnosis or hospitalisation for E10-E14 as an additional diagnosis where the principal diagnosis was any of the following: hypersmolarity (E87.0), acidosis (E87.2), transient ischaemic attack (G45), nerve disorders and neuropathies (G50–G64), cataracts and lens disorders (H25–H28), retinal disorders (H30–H36), glaucoma (H40–H42), myocardial infarction (I21–I22), other coronary heart diseases (I20, I23–I25), heart failure (I50), stroke and sequelae (I60–I64, I69.0–I69.4), peripheral vascular disease (I70–I74), gingivitis and periodontal disease (K05), kidney diseases (N00–N29) (including end-stage renal disease (N17–N19)) and renal dialysis (Z49). People with a hospitalisation for these conditions in the 12 months prior to study entry in both the exposed and unexposed groups were excluded from the study to minimise potential differences between the two groups in terms of diabetes severity and management.

Secondary outcomes included the examination of the rates of diabetes guideline-recommended care practices, including HbA1c test, microalbuminuria claims and claims for ophthalmology or optometry services, podiatry, dietician, diabetes educator and endocrinologist visits during the year following GPMP or index month. Subjects were followed-up until the primary study end-point, death or study end (30 June 2014), whichever occurred first.

Statistical analysis

Patient characteristics were compared between groups using *t*-tests for normally distributed continuous variables, Kruskal–Wallis test for non-normally distributed continuous variables and chi-square statistics for categorical variables. Risk of diabetes-related admission from time of GPMP in the exposed group and matched index month in the unexposed group were examined using

the cumulative incidence function, which takes into account the competing risk of death.[16] Gray's test for equality of the cumulative incidence functions was used to compare the risk of diabetes-related admission between the two groups. A Cox proportional hazards model was used to estimate hazard ratios (HR) for diabetes-related admission and the outcome of death, adjusting for a number of covariates (described below). Poisson regression analysis (taking into account follow-up time) was used to compare differences in the rate of recommended services for diabetes following exposure to a GPMP. Comorbidity was examined using a medication-based index, the Australian adaptation of the Rx-Risk-V index,[17] in the 6 months prior to the study. The models were adjusted at the time of GPMP or index month for patient age, gender, socioeconomic index for areas, region of residence (remote, outer regional, inner regional and major city), number of prescriptions and prescribers in the prior 12 months, one or more hospitalisations in the 12 months prior, changes in medicines (in the first 6 months after GPMP or index month compared with the last 6 months) and dispensing of adjunct cardiovascular medicines recommended in diabetes guidelines[18] in the year before the GPMP or index month. Given the evidence that home medicines reviews by an accredited pharmacist are effective in delaying time to hospitalisation in those with heart failure or warfarin users,[19,20] the results were stratified by patients who had had a claim for a home medicines review (MBS codes 900, 903) prior to the GPMP. A sensitivity analysis examining the risk of the next hospitalisation between the two groups for a diabetes-related condition with a principal diagnosis only (ICD-10AM E10-E14) was also conducted.

SAS version 9.1.3 (SAS Institute, Cary, NC, USA) was used to undertake all analyses.

Results

A total of 16 214 patients with diabetes was included in the study; 8091 had a GPMP, and 8123 did not have a GPMP. Demographic and clinical characteristics of the two groups are presented in Table 1. People who had a GPMP were more likely to be female (42% compared with 36% who did not have a GPMP) and live in an area of poorer socioeconomic status ($P < 0.0001$). People who had a GPMP had a greater number of prescriptions in the 12 months prior (median 72 (IQR, interquartile range) 50–100 vs 64 (IQR 42–93)), a slightly higher number of GP visits and greater use of health services, including health assessments, medication review and diabetes cycle of care in the year prior, in comparison to people who did not have a GPMP ($P < 0.0001$).

During the study period, a total of 1178 (7.3%) of the study cohort was hospitalised for a diabetes-related complication, and 1381 (9.7%) died. After 365 days, 6.7% (95% confidence interval (CI) 6.18–7.27) of those exposed to a GPMP compared to 7.8% (95% CI 7.25–8.41) of unexposed participants had a diabetes-related hospitalisation. Figure 1 depicts the cumulative incidence function curves for the two groups and shows a significant increase in the time until hospitalisation for a diabetes-related hospitalisation among people who had a GPMP compared to people who did not (Gray's test $P = 0.006$). After adjusting for covariates, a 22% reduction in the risk of having a diabetes-related hospitalisation (adjusted HR 0.78, 95% CI 0.69–0.87, $P < 0.0001$) was observed among people with diabetes who had a GPMP compared to people with diabetes who did not (Table 2).

Stratification of the analysis by prior medicine review found that people with diabetes who did not have a prior medicine review but had a GPMP had an 18% reduction in the risk of a diabetes-related hospitalisation (adjusted HR 0.82, 95% CI 0.73–0.93). In subjects with a prior medicine review and a GPMP, a 34% reduction was observed (adjusted HR 0.62, 95% CI 0.34–1.13), but this was not statistically significant (Table 2). Sensitivity analysis examining the risk of hospitalisation for diabetes as a principal diagnosis only found very similar results, with a 22.5% decrease in risk of hospitalisation (adjusted HR 0.78, 95% CI 0.69–0.88) for those who had a GPMP in comparison to those who did not.

For people with diabetes who had a GPMP, there was a significant increase in the utilisation of all diabetes-related recommended services, except for endocrinologist visits, in comparison to people with diabetes who did not have a GPMP (Table 3). This ranged from a 12% increase in the rate of ophthalmology/optometry visits (adjusted rate ratio (RR) 1.12, 95% CI 1.08–1.16) to a 530% increase in the rate of visiting a diabetes educator (adjusted RR 6.30, 95% CI 5.56–7.15). The examination of key diabetes pathology tests found a 29% increased rate of HbA1c testing (adjusted RR 1.29, 95% CI 1.25–1.33) and a 65% increase rate of microalbuminuria testing (adjusted RR 1.65, 95% CI 1.58–1.72) following a GPMP, compared to those who did not have a GPMP.

Discussion

This study provides evidence that the use of a GPMP results in improved health outcomes in the older population with diabetes. Provision of a GPMP was associated with a 22% reduction in diabetes-related hospitalisation and increased utilisation of guideline-recommended medical services for diabetes in the

Table 1 Demographic and clinical characteristics of diabetes patients exposed and unexposed to a GPMP (n = 16214)

	Exposed to GPMP (n = 8091)	Unexposed to GPMP(n = 8123)	P
Demographics			
Age, median (IQR)	81 (74–81)	81 (71–84)	<0.0001
Gender, *n* (% female)	3416 (42.2)	2958 (36.4)	<0.0001
Location, *n* (%)			<0.0001
Major cities	4380 (54.1)	5091 (62.7)	
Inner regional	2545 (31.5)	1865 (23.0)	
Outer regional/remote/very remote	1057 (13.1)	931 (11.5)	
Socioeconomic status, *n* (%)			<0.0001
High	1785 (22.1)	2169 (26.7)	
Medium/high	1900 (23.5)	2017 (24.8)	
Low/medium	2154 (26.6)	1832 (22.6)	
Low	2127 (26.3)	1848 (22.8)	
Medicine-related characteristics			
Number prescriptions in 12 months prior, median (IQR)	72 (50–100)	64 (42–93)	<0.0001
Number of changes in medicines 6 months prior, median (IQR)	7 (4–10)	7 (4–11)	0.0004
Prescribers in 12 months prior, median (IQR)	3 (2–5)	3 (2–5)	<0.0001
GP visits in 12 months prior, median (IQR)	12 (8–18)	11 (7–16)	<0.0001
Use of health services in 12 months prior, *n* (%)			
Health assessment	1754 (21.7)	820 (10.1)	<0.0001
Medicine review	496 (6.1)	151 (1.9)	<0.0001
Practice nurse	3377 (41.7)	2112 (26.0)	<0.0001
Diabetes cycle of care	1964 (24.3)	876 (10.8)	<0.0001
Mental health plan	119 (1.5)	42 (0.5)	<0.0001
Use of ACE/ARB in 12 months prior	6309 (78.0)	5805 (71.5)	<0.0001
Use of diuretic in 12 months prior	2801 (34.6)	2857 (35.2)	0.46
Use of β-blocker in 12 months prior	2883 (35.6)	2827 (34.8)	0.27
Use of Ca^{2+} channel inhibitor in 12 months prior	2931 (36.2)	2784 (34.3)	0.009
Use of anti-platelet in 12 months prior	3991 (49.3)	3532 (43.5)	<0.0001
Use of statin in 12 months prior	6163 (76.2)	5414 (66.7)	<0.0001
Comorbid conditions/hospitalisations			
Count comorbid conditions (Rx-Risk), mean (SD)	6.1 (2.4)	6.0 (2.5)	0.0003
Any hospitalisation in the previous year	3818 (47.2)	4140 (51.0)	<0.0001

ACE/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; Ca^{2+}, calcium; GPMP, general practitioner management plan; IQR, interquartile range.

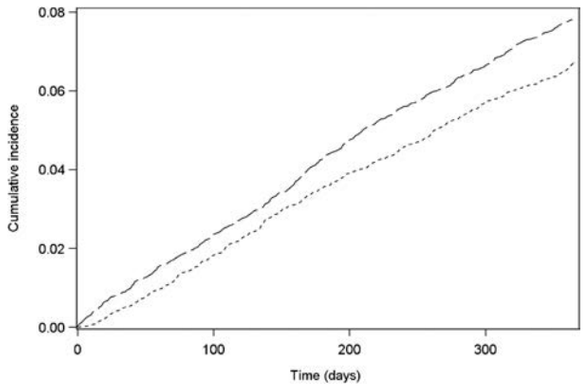

Figure 1 Cumulative incidence function showing time to diabetes-related hospitalisation among people with diabetes exposed (------) or unexposed (— —) to a general practitioner management plan.

following 12 months. With the annual cost of diabetes in Australia estimated to be A$14.6 billion dollars, with 43% (A$6.3 billion) being attributed to hospital inpatient care,[3,4] the provision of a GPMP in those with diabetes has the potential to result in considerable cost savings in addition to reduced morbidity.

A recent systematic review of the effects of care planning for adults with chronic conditions reported a small but positive effect on HbA1c levels in people with diabetes and their ability to self-manage their care when compared to usual care.[21] An Australian study has also shown that the provision of chronic disease management plans is associated with significant improvements in process and clinical outcomes for those with diabetes.[8] This included a 15% increase (95% CI 11.2–18.8%) in the proportion receiving guideline-recommended care and significant mean reductions in HbA1c levels, for example, by 2.4 (95% CI 0.3–4.5) from 55.8 to

Table 2 Association of exposure to a GPMP with time to diabetes-related hospitalisation

	Hazard ratio (95% CI)	*P*
No GPMP	Reference	
Exposed to a GPMP		
Unadjusted HR	0.82 (0.73–0.92)	0.0009
Adjusted† HR	0.78 (0.69–0.87)	<0.0001
Exposed to a GPMP and stratified by prior medication review		
No prior medication review		
Unadjusted HR	0.82 (0.73–0.93)	0.001
Adjusted† HR	0.79 (0.70–0.89)	<0.0001
Prior medication review		
Unadjusted HR	0.66 (0.36–1.20)	0.17
Adjusted† HR	0.62 (0.34–1.13)	0.12

†Adjusted for age, gender, socioeconomic indexes for areas, region of residence, number of comorbid conditions, number of prescriptions, number of prescribers, number of prior hospitalisations, changes in medicines and use of adjunct cardiovascular diabetes guideline medicines. CI, confidence interval; GPMP, general practitioner management plan; HR, hazard ratio.

53.4 mmol/mol and total cholesterol by 0.3 (95% CI 0.1–0.4) from 4.6 to 4.3 mmol/L. Another Australian study demonstrated that for people with heart failure, a GPMP was associated with a 23% reduction in the time to the next potentially preventable hospitalisation for heart failure.[22] Despite these reported benefits of care planning, the utilisation of GP management plans or chronic disease management items is low among people with chronic disease, the rates being 26.1% in older Australians[10] and 28.6% in people aged 45 years and older with either heart disease, asthma or diabetes.[23] The complexity, administrative burden and a potential lack of integration between care providers has been attributed as contributing factors for the low uptake of chronic disease management care plans.[24] Encouragingly, it appears that of the chronic conditions, the use of care plans is higher in people with diabetes, with reports that between 36 and 45% of people with diabetes receive a care plan.[10,23] The need for specific patient education for

Table 3 Rates, unadjusted and adjusted rate ratios (RR) of diabetes-related processes of care in people with diabetes exposed to a GPMP compared to the unexposed group

	Exposed to GPMP (*n* = 8091)	Unexposed to GPMP (*n* = 8123)	*P*
$HbA1_c$			
Rate, count per year (95% CI)	1.55 (1.52–1.58)	1.18 (1.15–1.21)	
Unadjusted RR (95% CI)	1.32 (1.30–1.36)	1.0	<0.0001
Adjusted† RR (95% CI)	1.29 (1.25–1.33)	1.0	<0.0001
Microalbuminuria			
Rate, count per year (95% CI)	0.76 (0.74–0.77)	0.44 (0.43–0.46)	
Unadjusted RR (95% CI)	1.71 (1.63–1.78)	1.0	<0.0001
Adjusted† RR (95% CI)	1.65 (1.58–1.72)	1.0	<0.0001
Ophthalmology/optometry			
Rate, count per year (95% CI)	1.68 (1.65–1.72)	1.44 (1.40–1.47)	
Unadjusted RR (95% CI)	1.17 (1.13–1.21)	1.0	<0.0001
Adjusted† RR (95% CI)	1.12 (1.08–1.16)	1.0	<0.0001
Podiatrist			
Rate, count per year (95% CI)	5.45 (5.33–5.57)	4.29 (4.19–4.40)	
Unadjusted RR (95% CI)	1.27(1.23–1.31)	1.0	<0.0001
Adjusted† RR (95% CI)	1.22 (1.18–1.27)	1.0	<0.0001
Dietician			
Rate, count per year (95% CI)	0.41 (0.39–0.43)	0.22 (0.21–0.23)	
Unadjusted RR (95% CI)	1.87 (1.72–2.02)	1.0	<0.0001
Adjusted† RR (95% CI)	2.18 (2.01–2.36)	1.0	<0.0001
Diabetes educator			
Rate, count per year (95% CI)	0.11 (0.10–0.11)	0.02 (0.01–0.02)	
Unadjusted RR (95% CI)	6.71 (5.90–7.61)	1.0	<0.0001
Adjusted† RR (95% CI)	6.30 (5.55–7.15)	1.0	<0.0001
Endocrinologist visits			
Rate, count per year (95% CI)	0.42 (0.40–0.44)	0.49 (0.47–0.52)	
Unadjusted RR (95% CI)	0.85 (0.79–0.92)	1.0	<0.0001
Adjusted† RR (95% CI)	0.88 (0.82–0.94)	1.0	0.0004

†Adjusted for age, gender, socioeconomic indexes for areas, region of residence, number of comorbid conditions, number of prescriptions, number of prescribers, number of prior hospitalisations, changes in medicines and use of adjunct cardiovascular diabetes guideline medicines. CI, confidence interval; GPMP, general practitioner management plan.

diabetes self-management and government initiatives focusing on collaborative models of care for people with diabetes[22] may be driving this higher uptake of care planning for diabetes patients.

Prior research has shown that people who have a GPMP have greater numbers of comorbid conditions and prior hospitalisations than people who do not.[22] Comorbidity is common among people with diabetes, and at least half of all older patients with diabetes will have at least one comorbid condition that may cause a potential treatment conflict, adding to the complexity of caring for such patients.[25] The provision of a GPMP may provide an opportunity to perform a complete review of the patient's overall treatment and care strategies, together with the development of patient-centred goals to facilitate improvement in the quality of care and subsequent health outcomes.

Examination of the characteristics of people with diabetes who received a GPMP showed that they were of lower socioeconomic status, had a greater number of prescriptions dispensed and GP visits in the 12 months prior, possibly indicative of more complex care needs. In our study, patients who had a GPMP were more likely to have received a home medicines review. Home medicines reviews in Australia have been shown to delay the time to the next hospitalisation in people with heart failure and in people on warfarin.[19,20] The stratified analysis shows that after exclusion of patients with a home medicines review, the effect of the GPMP on diabetes hospitalisation remained relatively unchanged (adjusted HR 0.79, 95% CI 0.70–0.89), indicating that the beneficial effect of a GPMP is independent of a home medicines review.

This study was conducted using DVA administrative health data; however, the results are likely to be applicable to other older Australians. Age-specific comparisons of DVA Gold Card Holders with no service-related disability and the wider Australian population have shown similar rates of GP visits, use of prescriptions and hospitalisations per year.[26] In an attempt to reduce differences between the two groups with regards to diabetes severity, people with a prior diabetes-related hospitalisation were excluded from our study; however, residual differences between the two groups may still remain. Our primary outcome included diabetes-related hospitalisations, including both microvascular and macrovascular conditions from recorded primary and secondary diagnoses. However, results were unchanged in our sensitivity analysis examining hospitalisation for diabetes complications as the primary diagnosis only.

Conclusion

This study shows a significant reduction in the risk of hospitalisation for a diabetes-related complication among people with diabetes who received a GPMP, with a 22% reduction in the rate of hospitalisation. In addition, there was an increased utilisation of guideline-recommended services for people with diabetes. Provision of a GPMP improves health outcomes for older patients with diabetes and should be included as part of their routine primary care. The identification of potential barriers to the uptake of this collaborative service is required to improve implementation.

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BRIEF COMMUNICATIONS

Over-imaging in uncomplicated low back pain: a 12-month audit of a general medical unit

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Key words
back pain, imaging, indication, radiation, general medicine.

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Abstract

Low back pain is frequently encountered in hospitals and is a leading cause of disability, often involving costly imaging that exposes a patient to radiation. A retrospective 12-month audit at a South Australian tertiary hospital aimed to evaluate the frequency, modality and appropriateness of imaging in patients with low back pain. Results showed that the general medical unit was unnecessarily ordering imaging in 40% of patients who exhibited no indications warranting such a procedure. A standardised protocol is required to preventing clinicians from requesting imaging solely for the purposes of self-reassurance, patient reassurance or fear of litigation.

From 2012 to 2013, over 100 000 Australians were admitted to hospital with a principal diagnosis of back pain, with an average length of stay of 3.5 days.[1] Data show that around one-third of patients presenting with back pain receive imaging, suggesting significant hospital expenditure plus inherent risks to each patient from radiation exposure.[2] Limited Australian data exist regarding compliance with recommendations for imaging of patients with back pain, and very few randomised controlled trials have been conducted firmly to establish best practice criteria for imaging. Several peak bodies have published guidelines in this area, namely the American College of Radiology (ACR), the European National Institute for Health and Care Excellence (NICE) and the Australian National Health and Medical Research Council.

It has been shown that low back pain without complications is a self-limiting and benign condition that does not require further imaging. The best practice is to treat such patients with reassurance and appropriate pain relief, following a comprehensive history and physical examination.[3] The recommendations for best practice are unanimous in that early imaging studies in uncomplicated back pain are unnecessary[2–4] unless the history and physical examination highlight certain factors that warrant further investigation. These are known as 'red flags' and may be representative of a serious underlying pathology.

The economic impact of a particular intervention or investigation must be considered in clinical practice for the sustainability of a health system. A study by Walker *et al.* estimated the cost of imaging in Australia for low back pain in the year 2001 to be greater than $66 million. To include the cost of inpatient care would increase the estimate to over $240 million.[5] Thus, reducing the frequency of unnecessary imaging in low back pain could result in significant economic savings.

Flinders Medical Centre (FMC) is a tertiary public teaching hospital in South Australia with 580 beds, comprising a general medical unit with four general medicine inpatient teams and two acute medical unit teams. A formal protocol for determining the need for imaging of low back does not currently exist at FMC. Hence, it was essential that an audit be conducted examining whether best practice is occurring within general medical teams at FMC managing presentations of this highly prevalent condition.

A retrospective audit was conducted of patients admitted under any of the general medical teams at FMC from 1 January to 31 December 2014. This type of study allowed for a longer time period to be evaluated and allowed for unbiased auditing of clinical decisions based on documentation. The FMC epidemiology department was consulted to provide a list of all patients admitted under general medicine in the 2014 calendar year with either a principal diagnosis or secondary diagnosis during admission of the International Classification of Diseases, Tenth Edition codes seen in Table 1.

The list of patients was provided to the FMC department of medical records, and patient case notes were subsequently reviewed over a 1-week period and included the retrieval of information from FMC's Open

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Table 1 ICD-10 codes used to derive the patient population requiring imaging for low back pain

ICD-10 code	Diagnosis
M51.0	Lumbar and other intervertebral disc disorders with myelopathy
M51.1	Lumbar and other intervertebral disc disorders with radiculopathy
M51.2	Lumbago due to displacement of intervertebral disc
M54.4	Lumbago with sciatica
M54.5	Low back pain

ICD-10, International Classification of Diseases, Tenth Edition.

Architecture Clinical Information System, especially for the confirmation of radiological imaging. Due to inpatient status, several notes were not available at the time of data collection but were later requested and included in the study to minimise bias. The audit was approved by the Southern Adelaide Clinical Human Research Ethics Committee on the 27 April 2015.

Demographics and all audit criteria were entered into a standardised data abstraction sheet.

The ACR red flags[3] (listed below) were chosen as the most comprehensive set of features determining the appropriateness of imaging:

1 Trauma.
2 Unexplained weight loss.
3 Unexplained fever or history of infection (especially urinary).
4 Age >50 years old, with osteoporosis or known crush fracture.
5 Immunosuppression or diabetes mellitus.
6 History of intravenous drug use.
7 History of cancer.
8 Prolonged use of corticosteroids.
9 Age >70 years old.
10 Focal neurologic deficit or signs of cauda equina syndrome.
11 Recent surgery.
12 Duration of pain six weeks or greater.

The FMC General Medical Unit was audited against the following:

1 Imaging should not be offered in patients with uncomplicated low back pain of less than 6 weeks duration.
2 If cauda equina syndrome is suspected, immediate magnetic resonance imaging (MRI) should be obtained.
3 Plain radiograph is indicated in any patients with a red flag/s (excluding cauda equina suspicion).
4 If plain radiograph is inconclusive, MRI can be considered, or computed tomography (CT) if MRI is contraindicated.

A total of 146 admissions from 132 patients was audited, with the mean age of admissions being 60 years and the average length of stay 6.1 days. Of the 146 admissions, 84 of these received imaging (58%), with 20 admissions receiving two different modalities. There were 52 lumbosacral plain radiographs, 33 MRI scans and 24 CT scans performed. A total of 103 admissions (71%) involved a patient with one or more red flags. Of these patients, 46% received imaging. Of the five patients sent directly to MRI for suspicion of cauda equina syndrome, only one was found to be positive. A total of 36 patients in the audit had one or more red flags but did not receive any imaging. Figure 1 shows the primary indicators for imaging, with trauma being the most frequent indicator.

Of the 146 admissions, 43 (29%) did not exhibit any red flags. Of these 43 admissions, 17 (40%) went on to receive imaging unnecessarily, regardless of the fact that their back pain did not warrant further imaging at the time. A total of 14 patients who received imaging unnecessarily (82%) was found to have either no pathology or no change in their mild degenerative disease. The remaining three patients were found to have lumbar disc displacement with radiculopathy; however, they still received supportive management and were discharged home with analgesia. Hence, 100% of imaging that was given unnecessarily did not change the management plan of that patient.

To quantify the economic expenditure of unnecessary imaging in this audit, the cost of imaging modalities was sourced from the Medicare Benefits Schedule. The price of an individual lumbosacral plain film, CT and MRI is $77, $240 and $348 respectively.[6] Hence, over $21 000 was spent at FMC in 2014 on imaging for low back pain, not including the associated costs of staffing and time spent in hospital awaiting scans. Looking specifically at

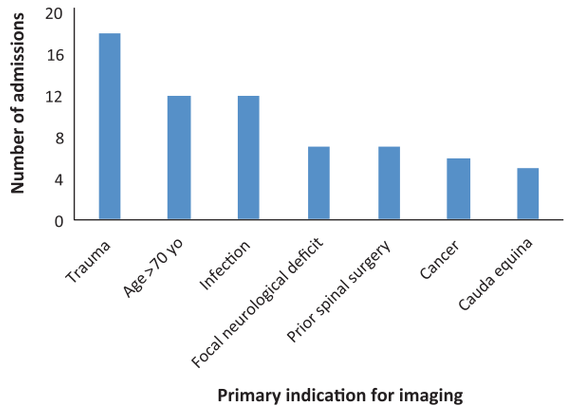

Figure 1 Distribution of primary indicators for imaging in admissions under general medicine at Flinders Medical Centre in 2014 with a diagnosis of back pain.

plain radiographs, almost $1500 was spent unnecessarily. Considering other departments (especially the emergency department) and the cost of unnecessary CT and MRI, this figure would be significantly higher if evaluating at the hospital as a whole.

The results from this audit show that as a whole, the FMC General Medical Department may be over-utilising imaging in low back pain. A total of 43 patients was admitted under general medicine at FMC in 2014 with no ACR-defined red flags, making it less likely for these patients to have a serious underlying pathology causing back pain. However, 40% of these patients went on to have imaging regardless. A systematic review and meta-analysis published in the *Lancet* in 2009[7] examined clinical outcomes in patients with back pain comparing whether or not they received imaging in the absence of red flags. Their results did not show any significant differences in outcome. They hypothesised that factors, such as patient reassurance, clinician over-cautiousness/self-reassurance and the desire, to identify a specific anatomical diagnosis contributed to the excessive ordering of imaging in back pain.

A total of 36 patients in the audit had one or more red flags but did not receive any imaging, with almost 50% of these being conservatively managed with physiotherapy input and simple analgesia as a result of known chronic back pain. Others had been recently investigated with imaging, were reviewed by the chronic pain team, started on neuropathic pain medications or were down-transferred for ongoing conservative management. In this subgroup, the main red flags were age greater than 70 years and previous spinal surgery (e.g. fusion). Hence, clinical reasoning was used to prevent these patients with chronic back pain from receiving imaging unnecessarily.

A randomised controlled trial from 2008[8] evaluated whether spinal imaging conducted purely for the purpose of patient reassurance altered patient outcomes. The study involved 246 patients with acute low back pain (without red flags) followed up over a 24-month period following an admission where they either received imaging or did not receive imaging. The data showed that patient outcomes were not altered from the control group, and in fact, the imaging group was associated with a lesser sense of well-being.

A positive finding of the audit was the immediate response and request for MRI if cauda equina syndrome was suspected. All patients suspicious of cauda equina (five in total) went straight to MRI without receiving lumbosacral plain radiograph, following best practice guidelines, although only one patient showed evidence of cauda equina on MRI. However, MRI was over-used in the younger population, who often skipped the lumbosacral plain radiograph when exhibiting a red flag other than suspicion of cauda equina syndrome.

An imaging flowchart was developed for implementation at FMC and is available upon request to the authors. Following evaluation with the departments of neurosurgery, rheumatology and neurology, we aim to introduce the flowchart algorithm and repeat the audit after a trial to assess its validity. The audit was limited by the inference of reasoning assumed for each admission and the relatively small cohort. Future research should focus on the evaluation of indicators for imaging, to avoid exposing patients to unnecessary radiation and to reduce the cost of healthcare

Acknowledgement

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Elderly patients are at high risk of night-time admission to the intensive care unit following a rapid response team call

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Abstract

Previous studies have shown that elderly patients (age ≥65 years) are less likely to be admitted to the intensive care unit following a rapid response team call and have high hospital mortality rates. This study has shown that elderly patients have a significantly higher probability of being admitted to an intensive care unit following a rapid response team call at night than during the day. However, at no time are they at greater risk than younger patients of incomplete vital sign recording, a failure to escalate care for acute deterioration or mortality.

Previous studies[1,2] have shown that there is a diurnal variation in the activity of the rapid response teams (RRT) and that elderly patients (age ≥65 years) are less likely[3] to be admitted to the intensive care unit (ICU) following a RRT call and have high hospital mortality rates. Elderly patients are also more likely to exert pressure on acute care resources by virtue of their illness acuity, burden of care, complexity and chronicity.[4] Whilst these age-based outcomes might be expected, age alone is rarely the only explanation. Elderly patients are at risk of healthcare rationing wherein less expensive treatment is offered to them, compared with younger patients with the same illness.[4] For example, overnight, when fewer experienced hospital staff are on duty, the elderly patient may receive less consistent care than younger patients. This may include less frequent and less intense monitoring, failure to respond to triggers of acute patient deterioration or fewer escalations of care, such as transfer to an ICU.

This situation may be compounded by the fact that several pathological states, common in an elderly patient, manifest as acute clinical deterioration at night. For example, hypertension, atrial fibrillation, myocardial infarction, stroke, obstructive sleep apnoea, cognitive impairment and endothelial dysfunction demonstrate circadian variation.[5] Similarly, this pattern of circadian variation closely mirrors that of RRT calls for sepsis, atrial fibrillation, seizures and pulmonary oedema.[6] If elderly patients fare worse at night, and this may, in part, be explained by exogenous and modifiable factors, then certain interventions can be employed with the aim of reducing diurnal variation in patient outcomes and optimising equitable quality healthcare irrespective of patient age.

Given the complex inter-relationship between the exogenous factor (i.e. diurnal variation) and the endogenous factor (i.e. circadian rhythm), there is a strong biological plausibility that patients, especially the elderly, would be at a high risk of acute deterioration and have worse outcomes during the night than during the day. However, available data are limited,[2,5] particularly with regards to the existence of diurnal variation in the monitoring of elderly patients in the ward (i.e. vital signs recording), in the response to clinical deterioration (i.e. afferent limb of the rapid response system), the failure to escalate to an RRT call when required (i.e. afferent limb failure (ALF)) and the need for an unanticipated ICU admission. Identifying whether elderly patients, who are at risk of clinical deterioration, exhibit a diurnal variation in their care would encourage

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the development of targeted interventions to improve their care around the clock.

The aims of this study were to elucidate diurnal variation in the admission of elderly ward inpatients (age ≥65 years) to the following a RRT call and to explore the relationship between age and the frequency of a complete set of patient observations, the number of RRT calls, afferent limb failure, ICU and hospital mortality.

Study design: A subgroup analysis of a prior published Point Prevalence study that sought to explore unplanned ICU admissions from the ward following a RRT call over a 2-day period in 2012 in 41 Australian and New Zealand ICU was undertaken. A night-time ICU admission was defined as an admission to the ICU between 18:00 and 07:59 h. Human research ethics committee approval was obtained for each site (HREC/12/RAH/157).

A total of 51 patients was admitted to the ICU from the ward following an RRT. Of these patients, 48 (94%) had complete data and were included in the analysis. A total of 24 (50%) patients was admitted following a RRT call for a cardiac arrest, and the remaining were admitted following a RRT call for another reason. Of the included patients, 32 (67%) were men, and overall the median APACHE II score was 21.0 (IQR 17–26). There was an association between age and time of admission to the ICU. Patients admitted to the ICU at night were older than daytime ICU admissions. The median age for patients admitted at night was 67 years (IQR 58–75) and during the day was 55 years (IQR 50–63) ($P = 0.01$).

For every 1 year increase in the age of the patient, the odds of night-time versus daytime ICU admission increased by 7% (odds ratio = 1.07, 95% confidence interval (CI): 1.01, 1.12). Night-time admission to the ICU carried no greater risk of ICU mortality (10/48; $P = 0.94$) or hospital mortality (17/48; $P = 0.53$).

Preceding the ICU admission, the overall prevalence of ALF was 18 (37.5%) and that of a complete 24-h set of vital signs was 23 (48%). A contingency table has been constructed to reflect these data (Table 1).

We used ordinal logistic regression analysis to investigate the association between RRT calls in the 24-h period prior to ICU admission and age and time of ICU admission (i.e. night-time/daytime). No significant interaction was found between age, time of ICU admission and number of RRT calls.

Discussion

We found that there is diurnal variation with respect to age and admission to the ICU following a RRT call, with increasing age being associated with the increased risk of an ICU admission at night. This diurnal variation was not accompanied by any increased night-time risk of afferent limb failure. The nocturnal frequency of the recording of vital signs was similar to daytime practice, and elderly patients were no more subject to these poor care quality outcomes than the younger patients. Patients admitted to ICU overnight had a similar mortality to those admitted during the day. Whilst elderly patients are less likely to be admitted to the ICU following a RRT call, the prognosis in the elderly and very elderly is generally limited; admissions to intensive care in these patients are often restricted despite the fact that a vast majority of elderly patients were discharged alive from hospital following treatment at the ICU, and more than half of them were still alive 1 year after their discharge.[7] The intriguing finding in our study is the preponderance for elderly patients to be admitted to ICU at night rather than during the day. There are several possible reasons for this variation in admission times across the 24-h cycle.

Circadian variation may manifest as a greater risk of acute physiological disturbance in the elderly at night, and, hence, precipitate an ICU admission. Similarly, diurnal variation in hospital resources, such as fewer senior medical staff overnight[8] and after hours, places elderly patients with complex medical problems at risk of not getting timely interventions.

Table 1 Vital signs recording and failure to escalate care in the elderly and younger patient population

	Age ≥65 years		Age <65 years	
	Night ICU admission	Day ICU admission	Night ICU admission	Day ICU admission
ICU admission preceded by ALF	6/12 (50%)	2/5 (40%)	4/13 (31%)	6/18 (33%)
ICU admission preceded by complete set of observations during the daytime	4/15 (27%)	1/4 (25%)	3/13 (23%)	4/16 (25%)
ICU admission preceded by complete set of observations during the night-time	5/15 (33%)	1/4 (25%)	2/13 (15%)	3/16 (19%)

First column identifies the care quality outcome and the other columns define the prevalence categorised according to the time of day of the ICU admission and the age of the patient. Numbers are the frequency of each adverse care quality outcome and the percentages are these numbers expressed relative to the total number of patients under each category. ALF, afferent limb failure; ICU, intensive care unit.

Finally, end-of-life decision-making, particularly with regards to promulgating documented advanced care directives (and avoidance of ICU admission), has more momentum when a senior practitioner (i.e. consultant /specialist) is present.[9] Given the current structure, wherein residents or doctors-in-training manage the hospital after hours under the remote supervision of the specialist, advance care decisions are being deferred[10] to the daytime when a senior practitioner is present. This deferral leads to the admission of some elderly patients to the ICU who would otherwise neither have needed nor secured an admission.[10]

We did not observe a diurnal variation amongst the elderly patients with respect to an increased risk for inadequate vital sign monitoring (i.e. incomplete patient observations) in the ward. Given the predilection for circadian destabilisation amongst the elderly, an increased calling of the RRT was expected; however, our study did not find a higher number of, or increased likelihood of, multiple RRT calls in the 24-h period preceding ICU admission amongst the elderly. Similarly, elderly patients were not at an increased risk of afferent limb failure and mortality (ICU and hospital), which mirrors the results obtained in a recent French study.[11] However, our inability to identify a relationship between increasing age and afferent limb failure and hospital mortality could reflect a β error, and a larger study is needed to answer this question definitively.

Being an observational study, our study was not adequately powered to detect a diurnal difference in mortality, afferent limb failure, number of RRT calls and frequency of completed observations. We were also unable to collect complete datasets on staffing levels and on the frequency of medical emergency team calls in the elderly over a 24-h period.

Implications: Given the increased demand on ICU resources for an ageing population[4,12] the clinical and administrative importance of diurnal variation in age at the time of admission to ICU cannot be underestimated and needs further evaluation.

Increasing age is a risk factor for an ICU admission at night. This might reflect a greater risk from circadian variation as manifested by acute physiological instability in the elderly or the risk from diurnal variation of hospital resources, particularly at night. Being elderly did not increase the risk for incomplete patient observations, multiple RRT calls, ALF and mortality at night compared to the day. A larger study is needed to explore further, and help better understand, these diurnal variations in admissions of elderly patients to an ICU.

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Documentation of consent for blood transfusion

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Abstract

In 2012, 110 hospitals reported on consent policy against national guidelines, with 105 (95%) including a statement on blood transfusion. Of the 103 hospitals (1788 transfusion episodes) that participated in the consent practice component, 89 specified the method of consent used; 46 (52%) had a specific transfusion consent form and achieved compliance of 90% compared to 43–69% for most other methods. The consent audit shows that a specific blood consent form achieved a high rate of medical record documentation compliance.

Informed consent for transfusion involves a conversation between a prescribing clinician and the patient receiving the blood product and includes the reason for the transfusion, the risks involved, the benefits and any alternative treatments available. It may include the provision of written information and an opportunity for the patient to ask questions. National clinical blood guidelines and healthcare accreditation clinical standards for blood and blood products require that informed consent for transfusion be obtained and documented.[1,2] Achieving consent documentation while ensuring it is not excessively onerous and consistent with existing hospital consent processes is desirable.

The Blood Matters programme, a collaborative between the Department of Health and Human Services, Victoria and the Australian Red Cross Blood Service, conducted an audit between August and December 2012 in Victoria, Tasmania, Australian Capital Territory (ACT) and Northern Territory (NT).[3]

Audit participation was voluntary and consisted of three sections:

- Hospital policy of blood transfusion consent: It was designed to determine if hospital consent policy for blood transfusion was consistent with the 'ANZSBT/RCNA Guidelines for the administration of blood products'.[1]
- Hospital blood transfusion consent practice: This included the collection of demographic information, clinical specialty, type of blood product transfused, whether consent was documented and who obtained the consent. Each hospital audited up to 30 individual, randomly self-selected medical records of transfused patients. This could be undertaken at the time of transfusion, any time during the admission or following discharge. No data were gathered to assess the institutional culture of documentation compliance.
- Patient survey to assess patients' (parent/guardian) understanding of consent: The survey focused on the patient's involvement and understanding of the consent process, engaging the patient or parent/guardian during the admission either at the time of transfusion, within 72 h of transfusion or prior to discharge. The results of this section of the audit will not be discussed further.[3]

The hospital transfusion committee or its equivalent was required to assign staff to collect and report data. Auditors were not trained; however, audit forms were accompanied with detailed definitions and instructions for conducting the audit, and Blood Matters staff were available to provide guidance and clarification throughout the audit. Auditors entered anonymous data electronically through the Blood Matters website through an online survey tool on a SelectSurvey ASP Advanced v.8.5.27 platform. Data were imported into a customised Microsoft Access database, where data were cleaned (reviewed for possible duplicates, incomplete data and other inconsistencies by Blood Matters staff) and descriptive analysis performed. Significance levels of bivariate associations between variables were assessed by chi-square tests, and when significant differences were observed, post hoc analyses were performed using Dunnett's *t*-test. Statistical computations were conducted

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with the statistical software package SPSS Statistics for Windows, Version 23.0 (IBM, Armonk, NY, USA).

Data review by Blood Matters staff (as described above) resulted in the exclusion of 25 records on hospital practice. Following data cleaning, individual hospitals received a summary report of submitted data and were given an option to address data errors.

A transfusion episode was defined as a minimum of a single unit/product transfused, either fresh blood components or fractionated products.

Our article focuses on data about existing hospital policy and reported compliance with documentation of consent. Of the 140 hospitals across Victoria, Tasmania, ACT and the NT invited to participate, 110 responded to at least one section of the audit (response rate 78%). A total of 103 hospitals was located in Victoria, 4 in Tasmania, 2 in NT and 1 in ACT; 82 were public hospitals, and 28 were private hospitals. A total of 44 was regional hospitals, 43 metropolitan and 23 rural (allocated based on the Australian Standard Classification Remoteness Areas, as published by Australian Institute of Health and Welfare).[4]

A total of 110 hospitals reported on the hospital consent policy, with 105 (95%) reporting a statement on blood transfusion. Of these 105 hospitals, 95 (90%) included a statement on how the informed consent should be documented.

The hospital practice audit reported on 1788 transfusion episodes submitted by 103 hospitals (17 episodes per hospital on average, range 1–30). The majority of episodes related to red blood cells (1636, 91%). Other products transfused included 68 (4%) platelets, 53 (3%) fractionated products, with fresh frozen plasma and cryoprecipitate making up the remainder (n = 31, 2%). In 547 of the transfusion episodes (31%), the patient received more than one blood product on the day, and where multiple products were transfused, the largest proportion was red cells. Overall, 1345 (75%) of the transfusion episodes reported valid documented consent.

Of the 103 hospitals responding to hospital policy and hospital practice, 99 (96%) reported a policy on consent, with 89 (86%) policies stating the method of documentation required (see Table 1). The most frequent documentation reported was a specific blood transfusion consent form (n = 46, 52%); other methods of consent documentation included a generic consent form with and without reference to transfusion (n = 18, 20% and n = 2, 2% respectively), a generic surgical consent form with reference to transfusion (n = 4, 5%), a medical record notation (n = 8, 9%) and a blood request form including a consent section (n = 2, 2%). The remaining 9 (10%) hospitals reported using multiple methods of documentation.

When transfusion was performed at a hospital with a reported policy on consent, 75% (n = 1291/1725) reported valid documented consent. For health services reporting no existing policy (n = 4), valid documented consent still occurred in 86% (n = 54/63) of cases. Hospitals with no existing policy did not have an opportunity (because of limitations of the audit) to specify what form of consent documentation they used.

Analysis of the method of consent documentation showed that the compliance of documented consent was significantly related to documentation type ($P < 0.05$). Hospitals with a specific blood consent form in place achieved the highest documentation of consent compliance of 90% (Table 1). Using Dunnett's t-test, with 'specific blood consent form' as the reference group, all other documentation types (except consent on the blood request form) had significantly lower consent compliance.

There was no significant difference (P = 0.12) in the compliance rates for those hospitals using a specific blood consent form and the hospitals' location: metropolitan 92% (n = 276), regional 88% (n = 355) and rural 93% (n = 95). Public hospitals accounted for 88% (637/726) of these episodes and had a higher compliance

Table 1 Method of consent documentation for transfusion and corresponding compliance rates reported by hospitals, 2012 Blood Matters audit of blood transfusion consent

Method of consent as stated in policy	Number of hospitals	Number of medical records audited	Consent documentation compliance (%)	Difference between means (95% CI)†	P
Specific blood consent form	46	726	90	Reference group	
Blood request form (including consent section)	2	40	88	−2% (±18%)	1.00
Surgical consent	4	58	69	−21% (±15%)	<0.05
Generic consent (with transfusion reference)	18	370	62	−28% (±7%)	<0.05
Multiple methods	9	196	61	−29% (±8%)	<0.05
Medical record	8	183	57	−33% (±10%)	<0.05
Generic consent (no transfusion reference)	2	30	43	−47% (±21%)	<0.05

†Dunnett t-tests treat one group as a reference and compare all other groups against it. CI, confidence interval.

Transfusion consent form template developed by Blood Matters

Disclaimer:
This is a guidance document only and organisations should seek independent legal and professional advice before using this document. Please refer to relevant local, state, territory or national acts and standards. Approval of this document should be undertaken through individual organisations governance processes.

****This template may be used in its current form or adapted as required by individual health services**

Informed Consent for Blood Transfusion Template

Unit Record Number: **Surname:** **Given Name:** **DOB** **Age: Sex:** **Affix patient Identification Label**	**Insert individual healthcare provider letterhead**

CONSENT FORM: Blood and Blood Products

DURATION OF CONSENT

** Incorporate a statement regarding length of time that consent is valid. It is recommended that this align with local hospital policy.

MEDICAL CONFIRMATION

I (enter name of doctor).....

Confirm that I have explained to patient/person responsible that.....may need transfusion or administration of blood or blood product:

(tick the appropriate box)

Fresh blood components ☐ red blood cells ☐ platelets ☐ fresh frozen plasma ☐ cryoprecipitate

OR

Plasma derived blood products

Please specify.....

I have explained

__ the reasons for transfusion/treatment
__ the risk versus benefits associated with the treatment,
__ the potential side effects and
__ the alternative treatments (if any).

Refer to http://www.transfusion.com.au for information on above mentioned points to be discussed with patient/person responsible.

The patient/person responsible has been given the opportunity to ask questions and have agreed to the administration of blood and/or blood products.

Printed Name of Doctor Signature of Doctor

Date..... ....

CONSENT

I, (insert name of patient/person responsible).....

Give consent for.....to receive blood and blood products by signing this form. I understand reasons for the treatment, probable effects and common risks as explained to me by the above mentioned doctor.

Signature of consenting person/legal guardian Date

.....

If a patient is not capable of consenting to his/her own treatment, consent should be obtained from the 'person responsible' (as defined in the *Guardianship & Administration Act* 1986), unless it is emergency medical treatment within the meaning of that Act)

Adapted from Southern Health Consent for Transfusion Form 2012

Your hospital may wish to include the following elements after approval from the hospital executive:

- a statement regarding the refusal of blood products

1

Figure 1 Transfusion consent form template developed by Blood Matters.

rate ($P < 0.05$) with consent documentation (93%, $n = 637$) than private hospitals using a specific blood consent form (67%, $n = 89$).

The National Safety and Quality Health Service Standard 7 requires the development and implementation of an informed consent protocol relating to blood and/or blood product transfusion, suggesting that consent be documented in the patient medical record and compliance with this documentation be audited. Where compliance is not achieved according to the protocol, actions to improve compliance should be undertaken. A transfusion consent form template with practice points is available at https://www2.health.vic.gov.au/hospitals-and-health-services/patient-care/speciality-diagnostics-therapeutics/blood-matters (Fig. 1).

Hospitals with a specific blood consent form achieve a high rate of documentation of consent for transfusion compliance and are therefore better able to align themselves with national guidelines and accreditation requirements. The introduction of a specific transfusion consent form would be one method of improving compliance and enabling the ongoing monitoring of compliance through audits of the medical record.

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Goodpasture disease as a consequence of melioidosis

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Key words
glomerulonephritis, Goodpasture syndrome, melioidosis, renal biopsy.

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Abstract

We describe a case of anti-glomerular basement membrane (GBM) antibody-mediated disease in association with concomitant *Burkholderia pseudomallei* (melioidosis) bacteraemia. The temporal profile of the illness and initial absence of circulating anti-GBM antibodies, in light of the subsequent definitive histological diagnosis of anti-GBM disease, makes this case interesting and unusual. Additionally, there have been no prior case reports suggesting melioidosis as a cause of biopsy-proven glomerulonephritis

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A 46-year-old Cook Islander presented to our hospital emergency department with a 1-week history of fevers, chills, myalgias, progressive shortness of breath and generalised abdominal pain. He also was anuric for several hours prior to presentation. He did not complain of arthralgias or rash. There was no history of recent travel, animal or freshwater exposure and no infectious contacts. He gave a history of smoking an average of 15 cigarettes per day for 20 years and admitted to intermittent alcohol abuse.

On examination, he appeared unwell and was pyrexial, with a blood pressure of 140/95 mmHg. A respiratory examination revealed bilateral basal crepitations, with radiological confirmation of alveolar airspace shadowing. His abdomen was soft but generally tender. There was no evidence of cardiac failure or peripheral oedema.

Biochemical analysis suggested evidence of severe renal failure with a serum creatinine concentration of 1600 μmol/L (reference range 73–108) and urea of 42.4 mmol/L (2.1–7.1). Liver function tests suggested cholestatic hepatitis (ALP 182 U/L (53–128), GGT 242 U/L (<55), ALT 67 U/L (<45), AST 54 U/L (<35)) with a mixed hyperbilirubinaemia (total bilirubin 96 μmol/L, conjugated bilirubin 59 μmol/L). Serum LDH was 694 U/L (150–280) and serum albumin 31 g/L (35–50). Full blood count showed a white cell count of 22.9×10^9, haemoglobin 134 g/L and platelets 114×10^9.

The patient was admitted to the intensive care unit (ICU) where he received veno-venous haemodiofiltration and empirical antibiotics consisting of meropenem and azithromycin for a presumed community-acquired pneumonia. The choice of antibiotic was dictated by his ethnic status and the tropical environment. Examination of his urine specimen (catheter collection) showed leukocytes $>500 \times 10^6$/L and erythrocytes $>500 \times 10^6$/L with no casts or dysmorphic red cells. Urine protein/creatinine ratio was 19 000 g/mol, consistent with nephrotic-range proteinuria. Serological tests for hepatitis B and C were negative. Additionally, serological tests for autoantibodies (anti-neutrophil cytoplasmic antibodies, anti-glomerular basement membrane (GBM) antibodies, serum complements (total, C3 and C4) and anti-streptolysin O titres) were all non-contributory. Anti-nuclear antibody, however, was elevated, with a homogenous titre of 160 of uncertain significance.

The patient subsequently required non-invasive ventilation for hypoxaemic respiratory failure. On day 3 of admission, blood and urine cultures grew *Burkholderia pseudomallei*, and intravenous meropenem was continued for a total of 6 weeks. Upon discharge from the ICU, he remained dialysis dependent, and upon achieving clinical stability, a renal biopsy was performed:

Light microscopic findings on 14 glomeruli showed large cellular crescents, some with breaks in Bowman's capsule, without necrosis or endocapillary proliferation. There was diffuse and heavy interstitial infiltrates of lymphocytes, macrophages and neutrophils. Acute tubular injury, along with the presence of red cell casts, was seen. There was no fibrinoid necrosis or vasculitis. An immunofluorescence examination showed heavy linear deposition of IgG along the GBM, along with mild granular deposition of IgM and C3 around capillary loops and in the mesangium. Electron microscopy showed glomerular compression by a large crescent with segmental sclerosis. There was wrinkling of the GBM, but it appeared intact. Foot process effacement was seen. There were also small subendothelial electron-dense deposits, without large subepithelial humps (Figs 1–3).

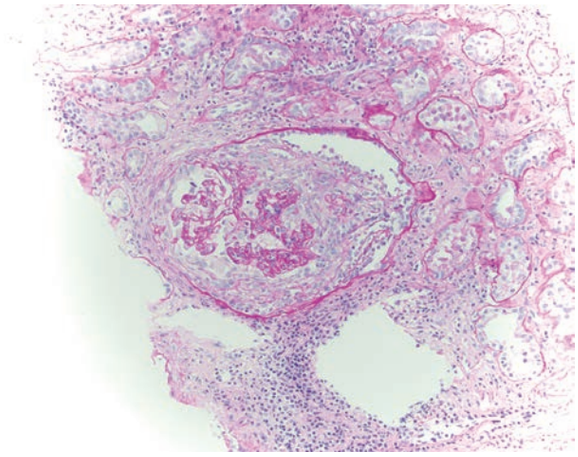

Figure 1 Light microscopy (periodic acid-schiff stain × 200) demonstrating large cellular crescents within the glomerulus and associated interstitial inflammation.

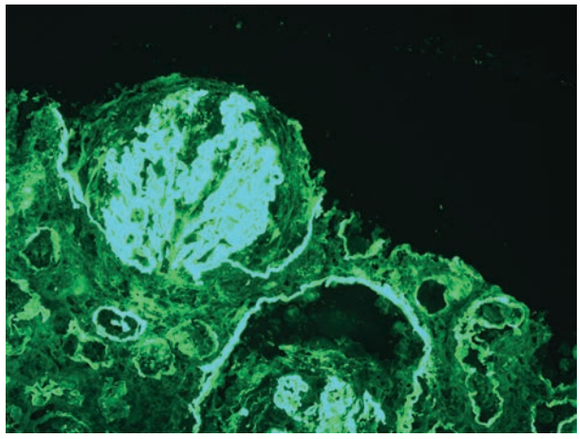

Figure 2 Immunofluorescence demonstrating heavy linear IgG deposition along the glomerular basement membrane.

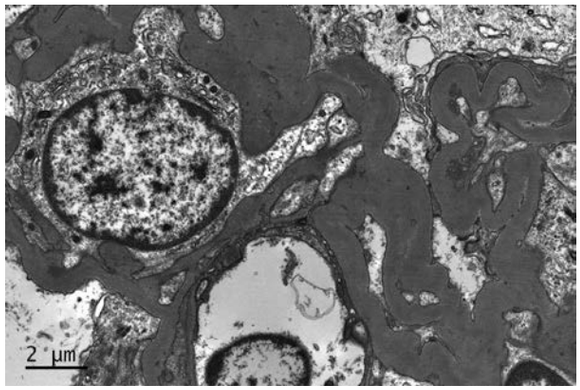

Figure 3 Electron microscopy demonstrating a large glomerular crescent with associated small subendothelial electron-dense deposits.

Thus, a diagnosis of anti-GBM antibody-mediated disease was considered very likely, and immunosuppression was initiated, consisting of intravenous pulse methylprednisolone (1 g daily for 3 days followed by 0.5 mg/kg of prednisolone daily) and oral cyclophosphamide (1.5 mg/kg daily). Serum anti-GBM antibodies were re-sampled. Interestingly, they were reported to be markedly elevated at 218 chemiluminescent units (reference range <20 CU). The initial sample was tested in parallel and again showed to be negative.

Three days after the renal biopsy, the patient developed respiratory distress and frank haemoptysis. This prompted treatment with therapeutic plasma exchange (TPE), which was continued daily for 14 days with complete clinical and radiological resolution. Blood cultures at this time were again positive for *B. pseudomallei* after having demonstrated negative blood cultures in the preceding weeks, and oral trimethoprim/sulfamethoxazole was added to his antibiotic regimen. Following TPE, his serum anti-GBM antibodies were 11 CU. He remains dialysis dependent 12 weeks after his initial presentation.

B. pseudomallei is a motile, aerobic, Gram-negative bacillus that causes melioidosis. It is an important source of human infection in parts of northern Australia, with a documented annual incidence in our health service district of 1.4 adult cases per 100 000; however, in the Torres Strait, the incidence rises to 42 cases per 100 000 population.[1] In southeast Asia, it is responsible for up to 50% of deaths because of sepsis. It is a soil saprophyte and can be acquired through direct inoculation or inhalation.[2] The lung is the most affected organ; however, the majority of cases present as acute septicaemia. Clinical features can range from a mild febrile illness to chronic abscess formation.

Melioidosis has important associations with renal disease. Chronic renal impairment specifically predisposes to infection, along with diabetes mellitus, chronic alcohol abuse and immunosuppression. Melioidosis can also cause acute kidney injury in 30% of cases, usually through acute tubular necrosis, interstitial nephritis and abscess formation.[3] One case of nephrotic syndrome in association with melioidosis was reported; however, no biopsy was performed, and causality was inferred based on the temporal profile of the illness.[4] To the best of our knowledge, there are no reported cases of glomerulonephritis manifesting as a consequence of melioidosis.

Anti-GBM disease is an autoantibody-mediated disease in which pathogenic antibodies are directed against the non-collagenous-1 domain of the α3 or α5 chain of type IV collagen. These molecules are found in specialised basement membranes throughout the body; however, clinical features are typically limited to the alveoli and glomeruli, whose basement membranes are the most easily accessible by circulating antibodies.[5] Goodpasture syndrome refers to the clinical pattern of alveolar haemorrhage and glomerulonephritis.[6]

Environmental factors are believed to play a role in triggering the disease. There have been localised clustering of cases, suggesting an infectious cause, and also reports linking anti-GBM disease to hydrocarbon exposure, influenza A2, organic solvents, cigarette smoking[7] and dengue fever.[8]

Diagnosis is based on the detection of circulating IgG antibodies, and false negatives are rare. These may occur in specific cases where non-IgG antibodies cause the disease (IgA or IgM), which are not detected using standard enzyme-linked immunosorbent assay or because circulating titres are too low for detection.[9] Definitive diagnosis is through renal biopsy, which shows characteristic linear IgG deposition on immunofluorescence and, occasionally, deposition by other immunoglobulin isotypes. Light microscopy will reveal cellular crescents. Electron-dense deposits on electron microscopy are usually not a feature of anti-GBM disease, although they may be found in the presence of a coexistent immune complex glomerulonephritis.[10]

In the case outlined above, the initial presentation is consistent with a diagnosis of anti-GBM disease; however, negative serological testing and the presence of a pathogen known to cause severe community-acquired pneumonia led to a delay in definitive diagnosis.

We postulate that the initial trigger for anti-GBM antibody production was melioid respiratory infection and the disruption of the alveolar basement membrane, which then cross-reacted with the GBM, causing rapidly progressive renal failure. The intensity of consumption of antibodies might explain why the initial serological test was negative. The subsequent development of a pulmonary haemorrhage with concomitant melioid bacteraemia and

raised levels of anti-GBM antibodies would support this hypothesis. In addition to this, small subendothelial electron-dense deposits seen on electron microscopy points to an immune complex aetiology. Whether this represents a coexistent immune complex glomerulonephritis or the entire process is as a result of the primary production of pathogenic anti-GBM antibodies remains conjectural.

In summary, this case adds to the literature regarding the possibility of the aetiological association of anti-GBM disease with systemic melioidosis. It also highlights the heterogenous nature of the glomerulonephritides with coinciding autoimmune and infectious aetiologies and features corresponding to both on microscopy.

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PERSONAL VIEWPOINT

From medical student to clinician-scientist: where is the pathway in Australia?

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Key words
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Abstract

Clinician-scientists are a valuable resource and are crucial to ensuring that high-quality health and medical research is undertaken and translated to patients. Although the literature notes the global decline in clinician-scientists and infers the worldwide similarity in the challenges to reverse this decline, Australia continues to lag behind in establishing an infrastructure to address the dilemma.

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Clinician-scientists are clinically trained health professionals who have undergone additional training in research and play a critical role in closing the gap between research and practice. Over the past two decades, there have been many research and editorial articles raising concern over the worldwide decline in clinician-scientists. Despite the efforts of many academic/clinician-scientists, Australia lags behind in establishing an infrastructure to begin to address this dilemma. The literature continues to infer that the decline in clinicians taking up research training and then establishing a career as a clinician-scientist is because of the mounting challenges faced in funding, curriculum design, mentorship and career pathway (USA[1], Canada[2], UK and Europe[3]). Interestingly Australia is rarely mentioned in any of this discourse.

Perhaps key to this issue here in Australia is the lack of a dedicated and linked national programme of funding, pathways or strategies for clinician-scientist training in both the undergraduate and postgraduate space. Most Australian medical schools offer a PhD or MPhil intercalated with the existing medical degree, as well as honours programmes and intermittent short-term research projects. However, there is no accurate consolidated source of information for these programmes or their outcomes apart from individual school websites. During the postgraduate years, research is encouraged and projects mandated though specialist training colleges, with some individuals opting to undertake a research higher degree during this time. Unfortunately, there is no coordinated approach incorporating a longer-term vision or pathway or incentive to attract and train outstanding students and place them on a clinician-scientist career track.

Ironically, the importance of integrating research into medical training has never been higher on the medical education agenda. This is, in part, because of growing requirements for the integration of research and clinical practice, rising competition for places in specialists' training programmes and the necessity to attract research funding. This perspective aims to challenge Australia's current position with respect to training future leaders in health and medical research. We offer suggestions to help bring Australia into the global dialogue on clinician-scientist training and pathways.

Is a Research Higher Degree necessary and when is the 'right' time?

The PhD is recognised as uniquely focused training in original research, under supervision, to develop a scientist with the competencies to undertake independent and responsible research that contributes to scientific discovery. It may be questioned as to whether a clinician needs a PhD to undertake research and contribute to scientific discovery.

Certainly, medical students are capable of combining substantial research alongside medical training, and this is both encouraged and facilitated in most medical programmes in Australia. This arrangement is seen as a means of boosting student career prospects and research experience through publications, which are of mutual benefit to students and research supervisors. This productive relationship is generally accomplished at a fraction of the administration, regulations, time constraints and expense of a PhD.

But here, we would add caution in considering this as a substitute for PhD training. The MD-PhD is a universal dual qualification in medicine. It is unique because it combines clinical and experimental training to organise a student's critical thinking. It is this combination that so specifically enables the insight that may translate research findings into practice. Furthermore, MD-PhDs have proven their general success in research and academia. Data from the US suggest that MD-PhD applicants are more successful in obtaining national funding than either a medical degree or PhD alone.[4] In keeping with the lack of infrastructure, there are few data from Australia regarding outcomes of medical student or physician PhDs. Traill *et al.* reported Physician PhD awardee data from Sydney Medical School and found an overall decline in PhD completions, low levels of research activity and publications among those who do complete, declining proportions of NHMRC funding to physician-led research and lower salaries in comparison to those in public hospitals.[5] Nevertheless, if one considers the 15 Australian Nobel Laureates, of the 8 that were awarded in medicine and physiology, 7 had either a human or veterinary clinical background.[6]

Clinician-scientist training models are primarily distinguished as being either undergraduate or postgraduate. It was William Osler in the late 1800s who drove the idea of the clinician-scientist, convinced that future advances in medicine and education would come from research.[3] As a result, the modern undergraduate model of combined MD-PhD training began at Johns Hopkins University in the 1950s, and the National Institutes of Health (NIH) began the Medical Scientist Training Program (MSTP) in 1964. The Canadian Institutes of Health Research (CIHR) set up a similar programme in 1995. In contrast, the undergraduate model is uncommon in the UK, but again, it was Osler's influence at Oxford in 1905 that precipitated a different pathway for clinician-scientist training

through the postgraduate years. This has most recently been improved through the Walport Report, which recommended an integrated and flexible career pathway throughout postgraduate training.[7]

The undergraduate model is universally acknowledged as 6–10 years of arduous training. It generally follows a 2 + 3–4 + 2 year model where intense research years are sandwiched between the pre-clinical and clinical years of the medical degree. A common argument for the MD-PhD, as opposed to a PhD during postgraduate training, is the notion of 'the earlier the better'. The MD-PhD graduate can begin using their unique skills and should hit the ground running for research during speciality training.

However, medical school is only the first step to completing medical training. Just where in the somewhat rigid and necessarily clinical postgraduate years will research fit in? Unfortunately, in Australia, there is no path or transparent structure waiting for medical students at graduation. This is a critical time to maintain research motivation or risk de-skilling new MD-PhDs. Furthermore, the absence of a pathway creates uncertainty and places multiple barriers in front of junior doctors willing to undertake a PhD or continue their research prior to, during or after specialist training.

Uncertain funding

There is no coordinated national funding for clinician-scientist training in Australia. Most medical students compete for PhD living scholarships through the Australian Postgraduate Awards, alongside every other postgraduate applicant in their university. These are exceptional students and often successful in gaining an Australian Postgraduate Awards, which helps with living expenses. However, the competition for static Commonwealth funds often means that even the most outstanding candidates miss out. Additionally, there is no relief on tuition for the medical degree and little recognition as a distinct student population with specific needs. For example, the increased time in training means a delay in earning potential by 3–4 years. Only the fortunate students receive additional funding from their supervisor, school or research centre through grants or fellowships.

In contrast, the MSTP funding in the US is designed as a package that incentivises the recruitment and retention process and ensures that the brightest and most committed candidates apply and are retained.[8] Students receive a fellowship that includes full MD tuition and a living stipend (approximately US $31 000/year) throughout the duration of the MD-PhD. There are 45 US medical schools participating in the MSTP. Participation is based on a university's research prestige and outcomes. This dedicated support through government funding sends a clear message that only the highest quality candidates and research-intense university medical schools are worthy of recognition and trusted to attract and build the country's clinician-scientist workforce.

Beyond medical school, there are various funding schemes available to support clinicians financially to gain a higher degree. These include sources such as the NHMRC and specialist colleges. Whilst valuable, it is likely that the primary inadequacy of these schemes lies in the 'stand alone' nature of the funding, with no coordination or link with clinical appointments and no connection to a broader pathway for the maintenance of clinical training and practice running in parallel with research.

Uncertain pathway

If we look to the NHMRC, there is obvious commitment to future health and medical research and its researchers through the extensive grant and fellowship schemes,[9] as well as the Commonwealth Government's new Medical Research Futures Fund.[10] Yet there is no advertised commitment to training in medical school or support to develop a clinician-scientist pathway. The current NHMRC structural project grant review makes minimal mention of clinician-scientists, with one of the proposals developed by an expert advisory panel including clinicians as a defined group within an 'alternative investigator-driven model'.

A pathway for training upon graduation and throughout the postgraduate years would help ensure the efficient use of skills and maintain research momentum whilst providing encouragement for new recruits. Continuity and flexibility in the early postgraduate years will help retain this skilled cohort and reduce barriers to those keen to pursue research after medical school.[11] In this respect, the postgraduate space could learn from the undergraduate intercalated MD–PhD model and the Walport Report.[7]

There are many issues that contribute to gaps in the continuum of medical and research training between the later years of medical school and early postgraduate years. Postgraduate years 1 and 2 afford minimal access to significant time and funds to continue research. During speciality training, there are opportunities through the colleges to begin a PhD programme, but again, depending on both funding and timing, new PhD graduates often find it hard to continue a research programme in conjunction with clinical commitments. The opportunity loss and cost incurred for clinicians with PhDs who never work as active researchers/academics are likely very large and currently underestimated. Possibly the greatest obstacles

include the lack of protected time, minimal flexibility, large discrepancy in salary rates of clinical versus research and no clear pathway to allow young medical scientists the opportunities to develop their research and medical careers in tandem. Given the 'time of life' in which postgraduate training occurs, the additional workload associated to undertaking both a research and a clinical load should not be underestimated. Individual life needs including family commitments must be considered. This is particularly relevant for women.[5]

'If we build it, they will come'

There is no shortage of Australian talent to take on the challenge of clinician-scientist training.[12,13] Global issues such as funding and supportive/flexible pathways continue to challenge the integrity of the clinician-scientist pipeline – which is long and leaky.[1] If we recognise that clinician-scientists are a valuable resource and are crucial to ensuring that high-quality health and medical research is undertaken and translated to patients, then we have an obligation to establish a funded and formal integrated pathway. We suggest that the NHMRC, speciality colleges, healthcare providers and universities engage in a coordinated manner to establish a connected, clear and funded pathway for clinician-scientists. Cooperation is required at all levels of medical training to ensure not just the preservation, but the resurgence of clinician-scientists in Australia.

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Clinical-scientific notes

Kimura disease in a Maori man with nephrotic syndrome

A 49-year-old Maori man with relapsing steroid-dependent nephrotic syndrome presented with progressive right post-auricular lymph node enlargement. There were no other palpable lymph nodes. A body computed tomography scan confirmed lymph node enlargement with no other lymphadenopathy. Excision and histology showed lymphoid hyperplasia, proliferation of small blood vessels and eosinophilic microabscesses. The biopsy was consistent with Kimura disease (KD).

The patient was first presented with the nephrotic syndrome at age 8, and he continued to have relapsing steroid-dependent disease. At age 10, a renal biopsy showed minimal change disease. He then received a course of cyclophosphamide with minimal benefit and was maintained on cyclosporine and prednisone to control his proteinuria with occasional bursts of high dose prednisone. A repeat biopsy at age 45 again showed minimal change disease. He had normal renal function with a glomerular filtration rate >90 mL/min and a bland urine sediment throughout the course of his disease. He had a normal protein electrophoresis, negative hepatitis serology, antinuclear antibodies and anti-neutrophil cytoplasmic antibodies. More recently, he had intermittent eosinophilia with eosinophils at 1.55 × 10E9/L (normal <0.5) and elevated IgE levels at 267 kIU/L (normal <100). A year after the excision of the lymph node, the patient's nephrotic syndrome remains in remission with small doses of prednisone and cyclosporine.

Kimura disease is a rare autoimmune eosinophilic inflammatory disorder affecting the lymphatic system; it presents predominantly in young Asian men with painless soft tissue masses of the head and neck.[1] Patients may also complain of pruritus and dermatitis. It is commonly associated with peripheral eosinophilia and elevated IgE levels.[2] The diagnosis is confirmed by lymph node biopsy, which is characterised by a benign angiolymphomatous proliferation with eosinophilic infiltration.[1]

Renal involvement occurs in 15–18% of patients with KD, with two-thirds presenting with nephrotic syndrome. Various glomerular lesions have been described with KD, including membranous glomerulonephritis (GN), mesangioproliferative GN, IgA nephropathy, IgM nephropathy, minimal change disease and focal segmental glomerulosclerosis (FSGS). Renal failure occurs in a minority of cases and mainly in those with FSGS.[1–3]

The pathogenesis of KD is not well understood. It has been proposed that viral infections or toxins alter T-cell responses or induce a type I hypersensitivity reaction, triggering lymphokine release resulting in the characteristic lymph node reaction and renal disease.[1]

The KD lesions often predate or coincide with the development of proteinuria.[1] The nephrotic syndrome predated the lymph node enlargement by approximately 40 years in our case. One may speculate that long-term steroid and cytotoxic therapy received for control of his renal disease played a role in delaying the appearance of the masses. The mainstay of treatment of KD and the nephrotic syndrome are corticosteroids and immunosuppressive agents.[3]

We report on the first case of KD in a Maori patient, and in this case, the nephrotic syndrome predated the KD lesion by many years. The patient responded to a combination of surgical resection of the soft tissue, systemic steroids and cyclosporine.

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Everolimus-induced tubular toxicity in non-renal cancer

Everolimus acts as a selective inhibitor of the mammalian target of rapamycin and is efficacious as both a post-solid organ transplant immunosuppressant and an anti-tumour agent through its known inhibition of the Akt-mTOR-p70S6K proliferative pathway in carcinogenesis.[1] Recently, the Pharmaceutical Benefits Scheme regulator in Australia expanded the indications for everolimus to the treatment of advanced breast, kidney and pancreatic neuroendocrine cancers at an initial fixed 10 mg daily dose, higher than that used for immunosuppression.[1] Whilst the nephrotoxicity of mTOR inhibitors has been demonstrated in patients with glomerulonephritis,[2] it is less recognised in the cancer literature.

In 2000, a 57-year-old Indian woman was diagnosed with hormone-positive, HER-2-negative stage IIa breast cancer, managed with a mastectomy, axillary clearance and chemoradiotherapy. She was treated with tamoxifen for 5 years. Her breast cancer recurred 10 years after diagnosis, which metastasised to her right hip, requiring radiotherapy. Subsequently, she was randomised to a clinical trial evaluating everolimus in breast cancer, which included a zoledronic acid arm, and was assigned to take both medications. She developed non-oliguric kidney damage over 2 weeks after being on the medications for 3 weeks. Baseline creatinine increased from 74 to 1200 μmol/L and urea from 8.6 to 46 mmol/L. Other relevant investigations were unremarkable. A renal biopsy was performed because of diagnostic uncertainty, showing extensive tubular epithelial injury characterised by cytoplasmic vacuolation, luminal shedding of cells, tubular dilatation and epithelial simplification (Fig. 1). Management included cuffed catheter placement for haemodialysis for a 3-week period, cessation of everolimus and zoledronic acid and sodium bicarbonate supplementation. Upon normalisation of her renal function, zoledronic acid alone was carefully introduced without deterioration in renal function. A rechallenge of everolimus 6 months after ceasing dialysis resulted in a second episode of haemodialysis over a 1-week period (serum creatinine 800 μmol/L). Unfortunately, chronic kidney dysfunction now remains (serum creatinine 160 μmol/L), independent of dialysis. Everolimus is no longer used, and her current chemotherapy is hormone-based.

Everolimus' only regulatory-approved indication in breast cancer is in the treatment of post-menopausal hormone receptor-positive, HER2-negative metastatic breast cancer in combination with exemestane (a steroidal aromatase inhibitor) after the progression of disease, following initial response to aromatase inhibition. The mechanism by which everolimus causes kidney failure appears to be tubular injury. Whilst experimental studies report that everolimus-induced injury targets the glomeruli and is dose-dependent,[3] preclinical studies are consistent with our finding of a reversible tubular injury. Nakagawa *et al*. found that the antiproliferative effects of everolimus in kidney epithelial cell lines occurred in the presence of the accumulation of the phosphatidylesthanolamine-conjugated form of microtubule-associated protein 1 light chain 3 (LC3-II), a marker for cellular autophagic activity in normal kidney epithelial cells.[4] The autophagy of tubular epithelial cells is a plausible mechanism of the tubular injury. Thus, this case shows that the acute kidney injury (AKI) is reproducible, and subsequent use of everolimus should be avoided. The expected toxicities of everolimus include stomatitis, diarrhoea, fatigue, anorexia, hyperglycaemia, hyperlipidaemia and pneumonitis. The treatment decision to use everolimus in breast cancer is complex, reconciling the competing oncological benefits and patient acceptance of the adverse events, which in this case was acute dialysis. Dialysis severely limits quality of life in this group, which has a short life expectancy. Therefore, the continuation of everolimus does not appear a sound risk/benefit decision.[5] Post-marketing reporting and clinician vigilance is critical for our understanding of the incidence of everolimus-associated AKI.

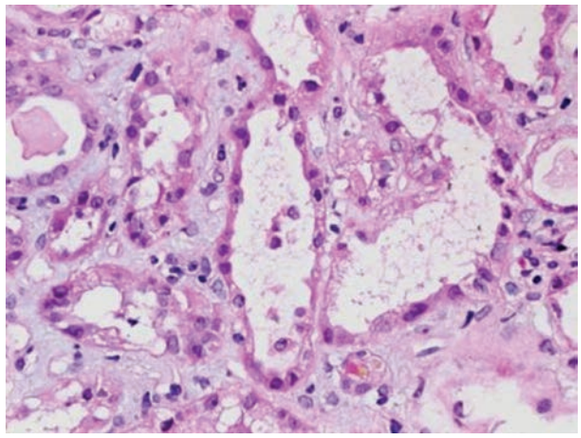

Figure 1 The renal biopsy showed tubular epithelial injury with epithelial cells containing clear cytoplasmic vacuoles, an irregular luminal surface and detached cells in the lumen. There is interstitial oedema without significant inflammatory cell infiltration (H&E, ×400 magnification).

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We sincerely thank the patient for allowing us to publish this case report.

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First reported case of khat cardiomyopathy and malignant hypertension in Australia

Khat is a drug of abuse used by millions of people, particularly in communities of the Horn of Africa and Arabian Peninsula. It causes multi-organ adverse health effects that are serious, and its import into Australia was only recently regulated. This case of reversible cardiomyopathy and malignant hypertension underlines the need for physicians caring for East African patients to enquire about khat consumption as part of a comprehensive health screening

A 37-year-old Eritrean migrant presented to our hospital with cardiac failure and malignant hypertension. Clinical history was notable for heavy consumption of khat; our patient chewed it recreationally with friends weekly and also intentionally for its amphetamine effect to stay awake in the night to watch international football games. He had additional cardiac risk factors of obesity (body mass index 37 kg/m^2) and ex-cigarette smoking (approximately 4 pack-years). There was no other medical history, and he took no regular medications or other illicit drugs.

On presentation, his blood pressure was 230/100 mmHg and his heart rate was 110 bpm. Troponin I was mildly elevated at 79 ng/L (normal <26 ng/L), and B-type natriuretic peptide was 311 ng/L (normal <100 ng/L). Screening for potential secondary causes of hypertension (including renin, aldosterone ratio, urinary cortisol and a vasculitic screen) was negative. Echocardiography demonstrated a dilated cardiomyopathy with severe biventricular systolic dysfunction (left ventricular (LV) ejection fraction 25%) and moderate functional mitral regurgitation. Coronary angiography revealed normal coronary arteries but confirmed severe global left ventricular dysfunction.

Our patient commenced appropriate anti-hypertensive and heart failure therapy in keeping with current management recommendations for methamphetamine cardiomyopathy and hypertension.[1] The likely antagonistic role of khat and the need for future abstinence was explained. Follow-up cardiac magnetic resonance imaging within 2 months of total khat cessation demonstrated near-complete recovery, with ejection fraction 48%, mild LV dilation, mildly increased LV wall thickness and no late gadolinium enhancement to suggest established fibrosis.

Khat (*Catha edulis*) is a leaf with amphetamine-type properties cultivated in East Africa and the Arabian Peninsula since the seventh century. It is estimated that there are 20 million users of khat worldwide, with khat chewing traditionally restricted to men.[2] Documented adverse health effects include psychosis, peptic ulcer disease, hepatitis, cardiomyopathy, accelerated coronary artery disease and malignant hypertension.[3,4]

Khat is classified by the World Health Organization as a drug of abuse and is illegal in the United States,

Canada and over half of the European Union. Until recently, licensed persons in Australia could legally import 5 kg per month for personal consumption; under these generous regulations, over 2000 kg was imported in 2008 alone.[5] In response to increasing community concerns (including a petition by women of the Australian Somali community), importation since April 2015 has now been restricted to scientific use.[2] Despite these new measures, khat usage anecdotally remains high within African communities.[3]

The East African community of Australia is now significant, numbering in tens of thousands of people.[3] Khat-induced hepatitis has already been reported in Australia,[4] and, with increasing migration, khat-related health problems are likely to become more prevalent in Australian healthcare settings. This case underlines the need for physicians caring for East African patients, particularly men, to enquire about khat consumption as part of a comprehensive health screening.

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General correspondence

Novel oral anticoagulant drugs and severe oesophagitis dissecans

It was interesting to read the articles by Baker *et al.*[1] indicating greater use of novel oral anticoagulant (NOAC) and Pattullo *et al.*[2] implying considerable uncertainty about appropriate dosing and prescribing of NOAC. We would like to report an uncommon but increasingly recognised complication of NOAC.

Dabigatran-induced oesophagitis is being increasingly recognised. A case series and several case reports have been published.[3,4] There have been no reported cases of erosive oesophagitis linked to other NOAC in the literature to date.

A 82-year-old woman presented to our hospital with a 2-day history of chest pain radiating into her back, odynophagia and 1 day of vomiting. She had been commenced on rivaroxaban for acute pulmonary embolus 8 weeks earlier and had a normal gastroscopy, which was done as part of the work up for pulmonary embolus and weight loss.

A computed tomography scan was performed to exclude an aortic dissection. Marked posterior mediastinitis and a distended oesophagus with solid debris were noted.

She went on to have a gastroscopy that showed longitudinal tears and desquamation of the entire oesophagus (Fig. 1), in keeping with severe oesophagitis dissecans (OD), along with food impacted upon the sloughed oesophageal tissue. The bolus was cleared and the patient was managed conservatively. Rivaroxaban was stopped

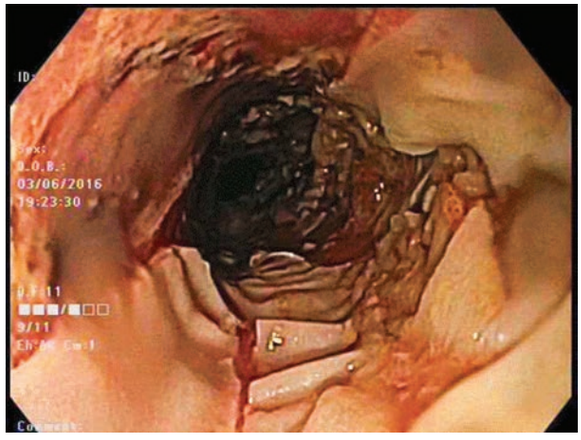

Figure 1 Oesophagitis dissecans on endoscopy.

and bridging therapy with enoxaparin used whilst she was converted to warfarin.

This is the first case of OD in the setting of rivaroxaban, but it bears many similarities to those described with dabigatran. Older age and oesophageal stasis appear to be risk factors.[5] Previous reports have suggested that the tartaric acid component of dabigatran may be responsible for increased mucosal irritation.[6] Rivaroxaban does not contain this, suggesting an unknown mechanism that may be unique to NOAC drugs.

Oesophagitis dissecans has been reported in association with other medications (bisphosphonates, non-steroidal anti-inflammatory drugs and potassium chloride), connective tissue diseases and bullous skin conditions (pemphigus and pemphigoid), but our patient did not have these risk factors.[7]

With increasing use of NOAC drugs especially in the elderly, clinicians need to be aware of this potential side effect.

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BOOK REVIEW

A History of Haematology. From Heroditus to HIV

By Shaun R. McCann. Oxford: Oxford University Press, 2016. 256 pp. GBP30.99; $US67. ISBN 978-0-19-871760-7

It is in the nature of ageing physicians that the history of their discipline becomes increasingly important. When a non-historian makes a decision to write a history of their area of specialisation, it is possible that this is in, part, a reflection of a desire to be a small part of that history thus being self-serving; however, I believe that such thoughts were far from the mind of this eminent author, well known globally in haematology from the period of time he occupied his academic chair in Dublin.

This book is the third of a planned series of volumes published by OUP under the banner of Oxford Medical Histories. The table of contents takes us on a journey from prescience through to what is termed the 'Enlightenment' highlighted by Harvey's description of the circulatory system in the 16th and 17th centuries. It is then a rapid jump to modern transfusion medicine to transfusion-induced HIV infection, the growing understanding of red blood cell morphology in health disease and a jump to haemopoietic stem cell transplantation in which the author played such an important part. Far from being a dry description of discovery, McCann takes us through the thought processes of the key discoverers as well as exploring the societal impact of things such as the altruism of donation of blood and stem cell products.

The chapter entitled 'The same specialty-but different approaches!' is a review of approaches to haematology discovery around the world: France, Germany, the USA, Sweden, the UK, Germany and Russia are contrasted with each other and the situation in India. In each geographic scenario, factors involved in training schemes and the nature of practice and investigation are detailed in an engaging way. The unifying theme is

the importance of the individuals in each jurisdiction who developed haematology in all of its subdisciplines according to local clinical needs. While the influence of German haematology was widespread, the depletion of medical talent by the deportation and extermination of many Jewish doctors during World War II altered the face of European medicine and haematology and the tragic behaviour of many German physicians during the war required a subsequent national apology. Russian haematology advanced in parallel with western nations along a somewhat different trajectory with different and unfamiliar (to us) names but reaching roughly the same places at approximately the same time. The formation of the European Haematology Association is described as a major unifying force in haematology in many countries, perhaps more successful than the political union of many of the same countries.

While the focus is largely on malignant haematology, blood banking, blood borne infective agents and modern molecular diagnostics and targeted therapies are not ignored. Neither are the technological advances which accompanied the explosion of knowledge acquisition and therapeutic ability in haematology.

This book is 200 or so pages of an easy and educational read with an eclectic and impressive set of references informing each chapter. Quotations from a diverse array of notable figures ranging from Thomas Jefferson, William Shakespeare and Mammon Chandy help to underline some of the major developments in this history.

Anyone with an interest in becoming or who already is a haematologist should acquire a copy of this book. Anyone else who has an interest in learning how to write an excellent and entertaining medical history should do the same.

J. Szer AM
The Royal Melbourne Hospital, Melbourne, Victoria, Australia

Corrigenda

The authors would like to draw the readers' attention to an error in the following article:

H. Quach, D. Joshua, J. Ho, J. Szer, A. Spencer, S. J. Harrison, P. Mollee, A. W. Roberts, N. Horvath, D. Talulikar, B. To, A. Zannettino, R. Brown, L. Catley, B. Augustson, W. Jaksic, J. Gibson and H. M. Prince. Treatment of patients with multiple myeloma who are eligible for stem cell transplantation: position statement of the Myeloma Foundation of Australia Medical and Scientific Advisory Group. *Intern Med J* 2015; **45**: 94–105. doi: 10.1111/imj.12640

The name of the author D. Talulikar should be spelt D. Talaulikar.

The authors apologise for the error.

The authors would like to draw the readers' attention to an error in the following article:

F. T. Roncolato, M. Chatfield, B. Houghton, G. Toner, M. Stockler, D. Thomson, M. Friedlander, H. Gurney, M. Rosenthal and P. Grimison, on behalf of the Australian and New Zealand Urogenital Prostate Cancer Trials Group (ANZUP). The effect of pulmonary function testing on bleomycin dosing in germ cell tumours. *Intern Med J* 2016; **46**: 893–898. doi: 10.1111/imj.13158

The following should be added on to the Funding section:

The Australian and New Zealand Urogenital and Prostate Cancer Trials Group is supported by Cancer Australia and Cancer Institute New South Wales. The online version of this article has been corrected.

The authors apologise for the error.

Erratum

The publisher would like to draw the readers' attention to an error in the following article:

A. McLaughlin. Coronary computed tomographic arteriography is anatomical and a myocardial perfusion is functional, detecting ischaemia – hence they are complementary. *Intern Med J* 2016; **46**: 991–992. doi: 10.1111/imj.13146

The word, 'study,' was omitted from the title of this article.

The title should read 'Coronary computed tomographic arteriography is anatomical and a myocardial perfusion study is functional, detecting ischaemia, hence they are complementary'.

The publisher apologises for the error.

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INTERNAL MEDICINE JOURNAL

Volume 46 2016
Volume Contents

Editor-in-Chief, Jeff Szer

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