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Centralising care for cardiac arrest survivors in Australia

Concentrating expertise in referral centres has been shown to be associated with improved outcomes in a number of conditions, both medical and surgical.\(^1,2\) Benefit is usually seen either where the condition is rare, such that most practitioners will have very limited experience with management or where there are technological or other complexities in management that would not be cost-effective to deploy widely. Quoting principally from evidence obtained overseas, in this month's *Internal Medicine Journal*, Stub and colleagues argue that survivors of out-of-hospital cardiac arrest (OHCA) in Australia are another group of patients that ought to have their care concentrated in specialist centres.\(^3\) OHCA is unfortunately relatively common, so transferring these patients to a few hospitals would require significant resources. Is there any evidence that outcomes from OHCA vary in Australia depending on the hospital to which a patient presents, and if so, what might be the explanations for this difference?

Data from the Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcomes and Resource Evaluation (CORE) Adult Patient Database show that the mortality rate for patients admitted to intensive care units (ICUs) in Australia and New Zealand from the Emergency Department (ED) with a diagnosis of cardiac arrest for the 3-year period 2009–2011 was 55.6% in tertiary hospitals, 61.7% in metropolitan hospitals and 51.4% in rural hospitals (Shaila Chavan, ANZICS, personal communication) (Table 1). The better outcome for patients in rural hospitals might reflect the effect of current practice to transfer more seriously ill patients direct from rural EDs to tertiary centres, but the worse outcome in metropolitan hospitals may support the authors’ contention that management of patients with OHCA in some hospitals is suboptimal. Should we then be moving to the establishment of cardiac arrest centres?

First, it has to be recognised that the main drop in survival following OHCA occurs at the scene. Survival from OHCA is related to the circumstances of the arrest, the availability and adequacy of bystander cardiopulmonary resuscitation (CPR), and the time to arrival of ambulance personnel with the capacity to deliver advanced resuscitation techniques such as defibrillation. In addition, achieving success in resuscitation will be impacted by underlying comorbidities in the patient. Some of the most impressive improvements in survival after OHCA have been following the deployment of automated external defibrillator (AED) machines in public places.\(^4\) Modern guidelines for bystander CPR have been significantly simplified such that most now recommend simple airway manoeuvres followed by chest compressions, and there is evidence that this can be easily taught to novices in the field with resultant improvement in outcomes.\(^5\) Provision of AEDs along with better education of the public regarding simple CPR and AED use may have the best effect on OHCA outcomes.

Once a patient with resuscitated return of spontaneous circulation following OHCA arrives in the hospital there are few proven clinical interventions that affect subsequent survival. Intuitively, close attention to simple matters such as airway management, oxygenation and ventilation, and support of the circulation should be

<table>
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<th>Year</th>
<th>2009</th>
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<th>Triennium</th>
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<td>17 457</td>
<td>14 513</td>
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<td>794</td>
<td>331</td>
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<td>Hospital deaths</td>
<td>441</td>
<td>198</td>
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<td>APACHE II predicted risk of death (mean)</td>
<td>0.73</td>
<td>0.71</td>
<td>0.69</td>
<td>0.73</td>
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<tr>
<td>Mortality (%)</td>
<td>55.5</td>
<td>59.8</td>
<td>54.9</td>
<td>57.2</td>
</tr>
</tbody>
</table>

Total admissions – total number of first ICU admission episodes entered into the database for each respective year. APACHE II predicted risk of death – APACHE II score predicted risk of death for cardiac arrest admissions. ANZICS, Australian and New Zealand Intensive Care Society; APACHE II, Acute Physiology Age and Chronic Health Evaluation II; CORE, Centre for Outcomes and Resource Evaluation; ICU, intensive care unit; NA, not applicable.
beneficial, but there is no evidence to guide us as to what targets we should set for such support. Recent work, for example, has suggested that increasing inspired oxygen concentration in the absence of arterial hypoxaemia may worsen outcome following myocardial infarction; however, following OHCA brain injury is the most frequent cause of death, and in this situation withholding oxygen might be detrimental. Therapeutic hypothermia is now advocated by most authorities that promulgate guidelines for the management of survivors of OHCA; however, while there are several studies demonstrating benefit of the therapy when compared with historical controls, there remains only two small prospective randomised controlled trials that clearly demonstrate benefit. Trials of initiating hypothermia in the field have thus far been disappointing. Various methods of initiating hypothermia have been evaluated; however, at present it would seem that simple external cooling plus use of cooled intravenous fluids is as good as more complex approaches. Evidence-based management of most survivors of OHCA in the ICU would appear to be relatively straightforward, therefore, and well within the capacity of metropolitan ICUs in Australasia.

In Australasia, we have had a unified training pathway for intensive care specialists since 2001 that employs a rigorous exit examination. The quality of intensive care training in Australia and New Zealand is recognised worldwide as second to none. As the output of qualified intensive care specialists has increased, the number of smaller hospitals that depended on anaesthetists, physicians or emergency specialists to cover intensive care services part time has decreased, and we are now not far from a situation where all hospitals with an ICU will have at least one Fellow of the College of Intensive Care Medicine on staff. Intensive care practice in Australia and New Zealand is thus more homogeneous than in most other countries, consequently, practice variation in the management of relatively common conditions such as OHCA is limited, and it would not be correct to suggest that many patients are treated in centres where the specialist’s experience is limited.

Where management will vary, however, is in access to complex interventions such as emergency coronary angiography and intervention, or to circulatory support in the setting of cardiogenic shock. Evidence for benefit of percutaneous coronary intervention (PCI) is only in patients presenting with ST-elevation myocardial infarction, but even in this group we should question the use of intervention where the chance of good neurological outcome seems remote. Predicting neurological outcome on patient presentation to hospital is very difficult, but careful review of the circumstances of the arrest, the length and complexity of resuscitation, clinical features of the patient on presentation, and the history of any comorbidities ought to ensure that resource use is targeted at those who are most likely to benefit. This requires an assessment at hospital of presentation, while a protocolised approach to transfer and intervention could possibly increase intervention in those not likely to benefit. Current practice in Australia in any case is for early transfer of patients from centres without access to early PCI where this is indicated, and this applies whether or not the patient presents following OHCA.

Mechanical support of the circulation in patients with shock following resuscitation from OHCA is more controversial. Survival after institution of mechanical support in patients without a readily remedial cardiac cause for shock is dismal. My personal experience of institution of venoarterial extracorporeal membrane oxygenation (ECMO) in a small number of patients undergoing CPR has been the prolongation of an undignified death with development of haemorrhage and multiple organ failure. The number of patients in whom aggressive support such as ECMO is likely to be useful is probably very small indeed and would not be a convincing argument to change the current practice in the management of patients following OHCA.

So where does this leave us with the issue of cardiac arrest centres, given the disparity in outcomes between tertiary and metropolitan hospitals suggested by the CORE data? Changing practice on the basis of possibly unrepresentative studies and a simplistic review of database outcomes is probably not warranted. The risk is increasing the expense and complexity of treatment without an improvement in outcomes. In Australia and New Zealand, even in the tertiary centres, over half of the patients admitted to ICU after OHCA do not survive to leave hospital. Transferring patients over long distances to die hooked up to various machines in an ICU far from home and family surely cannot be recommended unless it is clear that there is a worthwhile benefit. Evidence-based management of patients following OHCA is fairly straightforward for the majority of patients and should be possible in most ICUs, be they rural, metropolitan or tertiary. Before embarking on a change in strategy for these patients, we should at least audit the management and causes of death in patients in tertiary versus metropolitan hospitals so that we can better understand reasons why there might be disparity in outcome.

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Do we need cardiac arrest centres in Australia?

D. Stub, S. Bernard, K. Smith, J. E. Bray, P. Cameron, S. J. Duffy and D. M. Kaye

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Key words
cardiac arrest, systems of care, resuscitation, myocardial infarction, hypothermia

Abstract
The mortality rate post admission to hospital after successful resuscitation from out-of-hospital cardiac arrest is high, with significant variation between regions and individual institutions. While prehospital factors such as age, bystander cardiopulmonary resuscitation and total cardiac arrest time are known to influence outcome, several aspects of post-resuscitative care including therapeutic hypothermia, coronary intervention and goal-directed therapy may also influence patient survival. Regional systems of care have improved provider experience and patient outcomes for those with ST elevation myocardial infarction and life-threatening traumatic injury. In particular, hospital factors such as hospital size and interventional cardiac care capabilities have been found to influence patient mortality. This paper reviews the evidence supporting the possible development and implementation of Australian cardiac arrest centres.

Introduction
Out-of-hospital cardiac arrest (OHCA) is a common cause of cardiac death with an incidence in Australia of 148 per 100 000 persons per year. In a recent meta-analysis of over 140 000 patients with OHCA, survival to hospital admission was 23.8%, and survival to hospital discharge was only 7.6%. In patients who initially achieve return of spontaneous circulation (ROSC) after OHCA, the...
significant subsequent morbidity and mortality are largely due to cerebral and cardiac dysfunction that accompanies prolonged whole body ischaemia. This syndrome has been called the ‘post-cardiac arrest syndrome’ and comprises anoxic brain injury, post-cardiac arrest myocardial dysfunction, systemic ischaemia/reperfusion response and persistent precipitating pathology. Implementation of a comprehensive care plan for these patients has been shown to lead to improved outcomes\(^1\) and was recently promoted by the American Heart Association guidelines.\(^5\) However, delivery of systematic care for this patient population can be problematic because of administrative, resource and logistical barriers, leading to an underutilisation of important post-resuscitative interventions.\(^6,7\) Additionally, hospital factors such as hospital size and 24 hours a day interventional cardiac care capabilities have been found to influence patient outcome in Sweden,\(^8\) Japan,\(^7\) North America\(^10–12\) and Australia.\(^13\)

Despite these facts, patients resuscitated from cardiac arrest in Australia are not routinely hospitalised at specific cardiac centres,\(^13\) are cared for in many different intensive care units (ICU) and often receive care from teams with little experience in the management of these patients. Regional systems of care are well established for other time critical interventions in patients following trauma,\(^14,15\) stroke\(^16\) and ST elevation myocardial infarction (STEMI).\(^17\) Dedicated cardiac arrest centres have been established in North America\(^18,19\) and Europe,\(^20\) and in order to maintain optimal international treatment standards, urgent local research is needed into the implications of a regional system of care for patients resuscitated from OHCA in Australia.

**Trauma systems of care**

In the state of Victoria, a dedicated state-wide system of care for patients suffering traumatic injury was established in the year 2000.\(^21\) Key components of the system are highly trained emergency medical service (EMS), with triage guidelines that direct all patients with suspected major trauma to one of three major trauma services (MTS) if accessible within 30 minutes of the scene, and non-major trauma hospitals are advised to transfer patients to a MTS if patients meet criteria for major trauma. Another crucial aspect of the system was the development of the Victorian State Trauma Registry, a population-based registry collecting information on prehospital, in-hospital and post-discharge phases. Such data are important for guiding improvements in trauma management processes, and the registry has already highlighted a significant reduction in mortality and disability for patients treated in the Victorian trauma system.\(^14,15\)

**Systems of care for patients with myocardial infarction**

In a similar manner, there has been considerable progress in the development of models of care for patients with acute STEMI. These have evolved over a considerable period of time, including the creation of coronary care units and the development of mobile intensive care paramedic services. More recently, most states in Australia have adopted prehospital, EMS 12-lead electrocardiography (ECG) programmes in which patients with ST elevation on initial field ECG are transported directly to hospitals capable of emergency coronary intervention with field transmission of ECG and notification to cardiac team prior to patient arrival. Such programmes have been shown to reduce significantly door-to-balloon time, which is associated with improved patient outcomes.\(^22,23\)

The system of care for STEMI patients requires further development with regard to integration of non-metropolitan patients, data collection and monitoring systems but may provide a framework for the integration of patients with OHCA.

**Current state of cardiac arrest management in Australia**

Many states in Australia have highly developed EMS systems but with a wide variety of quality outcome reporting. For instance, in Victoria, the EMS consists of a two-tier system of advanced life support paramedics who are authorised to provide defibrillation, laryngeal mask airway insertion and intravenous administration of adrenaline. This is in addition to intensive care paramedics, who also perform endotracheal intubation and administer a range of additional cardiac drugs. A first responder programme by fire fighters operates for suspected cardiac arrest patients in the inner area of Melbourne,\(^24\) with a similar programme being currently piloted in outer regions. The cardiac arrest protocols follow the recommendations of the Australian Resuscitation Council.\(^25\)

Victoria has a well-established Victorian Ambulance Cardiac Arrest registry (VACAR) (>59,000 patient episodes) providing key data on prehospital care and patient outcomes.\(^26\) Since 2008, all OHCA patient care data are recorded electronically by the treating paramedics at the completion of the case and downloaded to a central server on return to the ambulance station. Cases of OHCA are identified, reviewed for completeness and recorded in the VACAR according to Utstein definitions.\(^27\)
Evidence for the regional systems of care for cardiac arrest

At present in Australia, patients with return of a spontaneous circulation (ROSC) after OHCA are transported to the nearest hospital with an emergency department, despite increasing data to suggest that the development of cardiac arrest treatment centres, may provide improved outcomes for the OHCA patient. A Japanese cardiac arrest register of over 10 000 patients showed that OHCA patients transported to critical cardiac care hospitals had improved 1-month survival compared with patients transported to hospitals without specialised cardiac facilities (6.7% vs 2.8%, \( P < 0.001 \), adjusted odds ratio 3.39, \( P < 0.001 \)). In a Swedish study of almost 4000 OHCA patients, there was marked variability in hospital outcomes after adjusting for prehospital factors, with survival varying from 14% to 42% in different centres. A US cross-sectional study of 109 739 patients indicated that hospital factors including teaching status, size and urban location were associated with outcome in patients resuscitated from cardiac arrest. Recent studies designed to optimise all facets of cardiac arrest care, including transport to dedicated cardiac arrest centres, have also been associated with improvement in outcomes.

The Take Heart America Program, a community-based initiative aimed at increasing OHCA survival, recently reported their results after the development of a regional system of cardiac arrest care for Minnesota. The programme involved optimisation of prehospital care including EMS and community training while also establishing protocols for transport to and treatment by three dedicated cardiac arrest centres providing therapeutic hypothermia (TH), coronary artery evaluation and treatment, and electrophysiological evaluation. When compared with historical controls, survival to hospital discharge improved from 8.5% to 19%, \( P = 0.01 \) (odds ratio 2.60, 95% confidence interval (CI) 1.19–6.26). Importantly, this outcome was driven by a dramatic improvement in survival after admission to intensive care (24% vs 51%, \( P = 0.011 \), with no significant improvement in rates of admission to ICU (35% vs 38%, \( P = 0.51 \)). A financial analysis revealed that the cardiac arrest centres concept was financially feasible despite the costs associated with the development of high-quality post-resuscitation care.

Another US-based programme, The Cool It Protocol, has also reported on the successful implementation of dedicated cardiac arrest centres being established from a pre-existing system of care for patients with STEMI. The Cool It protocol is a multidisciplinary system of care that affords regional and timely access to a standardised post-resuscitative care protocol through the rapid and coordinated transfer of patients to cardiac arrest centres. In their preliminary results of the first 140 patients who remained unresponsive post-ROSC, 56% of patients survived to hospital discharge with 92% of survivors discharged with a positive neurological outcome.

Conversely, the Resuscitation Outcomes Consortium investigators examined the outcomes of 4087 patients with OHCA. In that study, patients post-OHCA who were treated at hospitals capable of invasive cardiac procedures centres did not have increased rates of survival after adjusting for prehospital factors. Similarly, a recent retrospective analysis that combined quality improvement data from the Cardiac Arrest Registry to Enhance Survival registry evaluated the influence of hospital characteristics on survival in patients with OHCA of suspected cardiac aetiology. A significant relationship was observed between trauma centre designation but not presence of a coronary catheterisation laboratory or the volume of patients received, and survival or neurological outcome.

With regard to Australian data, we recently published results from Victoria using the VACAR registry highlighting that hospital characteristics were associated with patient survival. Our study examined 2902 patients who achieved ROSC and were transported to one of 70 Victorian hospitals. Two thirds (63%) of patients were treated at hospitals with 24-hour cardiac intervention services. After adjusting for differences in baseline characteristics, hospital factors significantly associated with survival were: treatment at hospitals with 24-hour cardiac intervention services (odds ratio 1.40; 95% CI 1.12–1.74, \( P = 0.003 \)), and patient admission between 0800 and 1700 hours (odds ratio 1.34; 95% CI 1.10–1.64, \( P = 0.004 \)). OHCA patient volume and total hospital bed numbers were not independently associated with outcome.

An important observation in our study was that increased transport time to hospital did not adversely affect outcome. This is supported by other studies indicating that increased transport time to facilitate transfer to a cardiac centre did not adversely impact on patient survival. Therefore, bypass of the closest hospital for transport to a cardiac centre may be appropriate in a regionalised system of care. Long transport times may be more significant in a rural Australian setting and consideration of developing dedicated rural cardiac arrest centres, akin with the recent development of rural percutaneous coronary intervention (PCI) services needs to be considered. However, the trauma system of care for rural patients in the state of Victoria has been highly successful.
Standardising post-resuscitative care

Aiming for improvements in post-resuscitative care at all treatment centres who care for patients post-OHCA is vital and represents a possible alternative to dedicated cardiac arrest centres. Treatments that are thought to improve outcome after OHCA resuscitation include therapeutic hypothermia (TH),32,33 early reperfusion of blocked coronary arteries34,35 and possibly optimisation of critical care parameters, such as blood pressure, glucose, and optimisation of oxygenation and haemodynamics.4 Cardiogenic shock in this patient population is common and associated with significant morbidity and mortality.36 In many instances, cardiac support with an intra-aortic balloon pump is inadequate to maintain adequate organ perfusion. As such, advanced cardiac support with percutaneous cardiopulmonary bypass with extracorporeal membrane oxygenation is an alternative option, with the additional benefits of possibly aiding resuscitation in prolonged arrest.37 These interventions require a multi-disciplinary team with experience and expertise in the management of these patients.

Post-cardiac arrest anoxic brain injury is a major cause of morbidity and mortality, and is responsible for approximately two thirds of the deaths in the post-cardiac arrest period.38 One important advance in post-ROSC management is the use of TH for the treatment of comatose survivors of OHCA. Two randomised, controlled trials have clearly confirmed the benefit of TH after cardiac arrest.32,33 Both studies investigated mild TH in comatose adult patients after OHCA secondary to ventricular fibrillation (VF). A subsequent individual patient data meta-analysis indicated the number of patients needed-to-treat to provide a good neurological recovery is six.39 As a result of these trials, the most recent American Heart Association guidelines recommend TH be induced as soon as possible and maintained for 12–24 hours in the management of anoxic neurological injury post-cardiac arrest when the initial cardiac rhythm is VF/ventricular tachycardia (VT) and suggests consideration of its use after resuscitation from OHCA when the initial cardiac rhythm is asystole or pulseless electrical activity.40

In addition to the induction of TH, early coronary angiography should be considered in patients with OHCA and successful resuscitation where it appears that there was a cardiac cause for the arrest. However, the role of early PCI in this group of patients is uncertain. There have been no prospective randomised trials in comatose patients post-OHCA examining the role of coronary angiography. However, there is considerable observational data that support the role of early angiography and PCI if needed in patients post-OHCA with STEMI.34,41

The role of primary PCI in patients who have been resuscitated from OHCA and who do not have STEMI on 12-lead ECG is uncertain. On the one hand, this procedure is expensive and would not be justified if the neurological prognosis was very poor.41 On the other hand, unstable coronary plaques suitable for treatment with PCI may be missed if decision-making is based on 12-lead ECG criteria alone.34,44 A recent study of cardiac arrest patients undergoing coronary angiography found significant coronary lesions occur in up to 66% of patients without ST elevation.45 The largest series of coronary intervention in the setting of OHCA has found that PCI was an independent predictor of survival irrespective of initial ECG findings (odds ratio 2.06, P = 0.013).46 Given the relatively good prognosis of patients who receive TH following OHCA and who have an initial cardiac rhythm of VF or VT, the difficulties of accurate early prognostication and the lack of sensitivity and specificity of the initial 12-lead ECG, it seems reasonable that all patients with coma following OHCA, and an initial cardiac rhythm of VF or VT, should undergo both immediate TH and early coronary angiography.46

Despite the evidence supporting the use of TH and PCI in the post-cardiac arrest patient, the uptake of these important post-resuscitative measures has been poor.6,7 Therefore, developing dedicated centres with standardised post-resuscitative treatment guidelines has the potential for significant improvement in patient outcomes. One of the early cardiac arrest centres in Europe developed a post-resuscitative care treatment protocol including TH, early PCI for ST segment-elevation myocardial infarction and early haemodynamic optimisation. In their initial intervention period, 26% of OHCA survivors admitted to the hospital with a pulse survived to discharge prior to implementation of the protocol, and this increased to 56% following implementation of the post-resuscitation care protocol (P = 0.001).4 A recent report indicated maintenance of this relatively good survival rate 5-year post-protocol implementation.50 Locally, we have shown at a large hospital with expertise in acute cardiac care that a contemporary post-resuscitation treatment strategy including TH and coronary intervention in patients admitted post-OHCA was independently associated with survival when compared with historical controls (odds ratio 5.5 95% CI 1.2–26.2, P = 0.03).53

Organisation of clinical care services

As with trauma and STEMI systems, many regions overseas are developing systems of care for patients with OHCA, incorporating dedicated cardiac arrest centres. In these regions specific criteria have been developed to enable categorisation, verification and designation of...
centres for the treatment of patients with ROSC post-OHCA (Table 1). These centres have commonly been founded on multidisciplinary collaboration including staff from emergency medicine, critical care, cardiology, respiratory and neurology. Much like trauma teams, many centres coordinate care through dedicated cardiac arrest referral teams. Together, these teams are responsible for initially stabilising the patients, making decisions on continuation or implementation of TH after hospital arrival, and helping to direct additional post-arrest care.

The development of a system of care for high-risk cardiac patients such as those with OHCA could potentially carry significant adverse implications for the cardiac arrest centre in terms of healthcare expenditure and non-adjusted patient outcome figures. Accordingly, given the importance of transparent clinical outcome reporting, the use of appropriate risk-adjusted quality estimates are necessary. With regards to healthcare costs, resuscitation interventions that increase survival have been associated with good quality of life and acceptable costs to society.

The data supporting implementation of cardiac arrest centres are predominantly observational and derived from international studies. Further research into the impact of developing a system of care for cardiac arrest patients in Australia is urgently needed. Studies with a focus on defining the relative contribution of prehospital and in-hospital factors, how cardiac arrest centres may be incorporated into pre-existing trauma and STEMI systems of care, and the implications on EMS services, hospital capacity, cost and longer term patient outcomes accompanied by quality of life measures are required. Based on the available evidence, however, the American Heart Association has recently recommended that regional systems of care be developed for patients with OHCA, and more specifically that within the context of a regional approach to acute interventional cardiology, patients with OHCA where the initial cardiac rhythm is VF or OHCA with ST segment elevation be transported directly to cardiac arrest centres.

### Table 1 Potential clinical services needed at Australian Cardiac Centres

<table>
<thead>
<tr>
<th>Clinical Service</th>
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<tr>
<td>Therapeutic hypothermia</td>
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<tr>
<td>24-h percutaneous coronary intervention service</td>
</tr>
<tr>
<td>Mechanical cardiac support services</td>
</tr>
<tr>
<td>Cardiac arrest consultation service</td>
</tr>
<tr>
<td>Ventilator management strategies</td>
</tr>
<tr>
<td>Electrophysiology/cardiac service</td>
</tr>
<tr>
<td>Neurology/neurosurgical consultation</td>
</tr>
<tr>
<td>Multimodal neuroprognostication diagnostic service</td>
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<tr>
<td>Physiotherapy/social work/occupational therapy</td>
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<tr>
<td>Neuropsychology service</td>
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In patients who achieve return of circulation after OHCA, morbidity and mortality remain significant. Treatment strategies focusing on both prehospital and post-resuscitative care are vital in improving patient outcomes and may be further optimised with the development of regional systems of care. Specifically, emphasis should be placed on the development of specialist cardiac arrest centres that offer goal-directed therapies including TH, early coronary angiography and temporary circulatory support where appropriate, together with comprehensive neurological assessment and therapy. We would call for urgent research into the efficacy and implications of establishing a regional system of care for patients post-OHCA in Australia.

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36 Lim HS, Stub D, Ajani AE, Andrianopoulos N, Reid CM, Charter K et al. Survival in patients with myocardial infarction complicated by...
CLINICAL PERSPECTIVES

Leukaemias into the 21st century: part 1: the acute leukaemias


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Key words
leukaemia, acute leukaemia, AML, ALL, therapy.

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Abstract
The leukaemias are a biologically and clinically heterogeneous group of malignancies, which manifest as clonal expansions of a single cell at different stages of lympho-haemopoietic development. The transformed cell acquires an unrestrained capacity for self-renewal and, in the case of the acute leukaemias, also fails to differentiate into functional mature cells. Historically leukaemias were classified using a combination of clinical and (presumed) cell lineage criteria. Thus, the four major subgroups of acute and chronic myeloid leukaemia and acute and chronic lymphoid leukaemia were recognised. Up until the last 10–15 years, patients within each major subgroup were treated along broadly similar lines. Genetic abnormalities have been recognised in certain leukaemias for over 50 years; however, the recent explosion in our understanding of the frequency and complexity of molecular abnormalities in the leukaemias has ‘opened the door’ for the design of more targeted therapies with the expectation that their incorporation into therapeutic regimens will be associated with greater efficacy and less off-target toxicity.
Introduction

Data from the NSW Cancer Institute demonstrate that in 2008, as a group, the leukaemias were the 11th most common cancer by diagnosis and ranked 12th in cancer-related deaths.¹ As the name suggests (white blood), the leukaemias are most readily recognised by effects on the normal bone marrow and/or peripheral blood with patients commonly presenting with manifestations of haemopoietic failure and/or the consequences of the accumulation of malignant cells. The current classification of the leukaemias is complex and outside the scope of this review. A detailed description of leukaemia classification can be found in the most recent World Health Organization (WHO) publication.² In the first part of this series, we review recent developments in the management of the acute leukaemias and a subsequent contribution will cover the chronic leukaemias. Our primary focus will be on the leukaemias encountered in adult practice.

The acute leukaemias

Clinically defined by a more rapid disease tempo, the acute leukaemias are those which progress over weeks to months ultimately culminating in bone marrow failure. Specific treatment is instituted soon after diagnosis unless precluded by age and/or significant comorbidities. In contrast, the chronic leukaemias have a less aggressive presentation and even untreated may have a prolonged clinical course.

Acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) result from acquired genetic defects that arise in early haemopoietic progenitors, which drive uncontrolled proliferation and disrupt normal myeloid or lymphoid differentiation programmes. Defects in earlier uncommitted haemopoietic stem cells are also recognised, which occasionally blur the distinction between AML and ALL. Gilliland proposed a model of leukaemogenesis in which cooperative mutations provide a proliferative advantage (type 1) complemented by mutations that disrupt normal cellular differentiation (type 2).³ In AML however, recently identified mutations that affect genes involved in signal transduction, apoptosis, epigenetic regulation, histone modification, and the spliceosomal machinery suggest that the pathophysiology of leukaemogenesis is much more complex with many more contributory genetic lesions than previously suspected.

ALL is the predominant leukaemia in childhood (<15 years). With increasing age the frequency of ALL as a proportion of all acute leukaemias declines, and AML is the more predominant adult acute leukaemia. While great advances have been made to improve the cure rate of paediatric leukaemia the same unfortunately cannot be said for most adult acute leukaemias, with the exception of the specific AML subtype, acute promyelocytic leukaemia (APL).

In AML, incremental gains in overall survival are being seen each decade although predominantly in younger patients (Fig. 1). This can be attributed in part to improvements in supportive care including transfusion support, better antifungal treatment and improved management of infection during the neutropenic period, rather than dramatic improvements in cytotoxic therapies per se. Management of acute leukaemia in adults therefore remains an area of unmet need in the 21st century.

Acute myeloid leukaemia

In the WHO classification, AML subtypes are defined on the basis of morphological, cytogenetic and molecular
criteria. The median age of onset is 66 years with approximately 70% occurring over the age of 55 years. The incidence of AML in Australia is 4/100 000 and increases with age to rates greater than 25/100 000 in people over 75 years. While in younger adults (generally defined as <60 years) overall cure rates approach 40–45%, AML in the elderly has a less favourable outcome with few long-term survivors. Age and fitness for treatment are therefore important factors in determining management for the individual patient. The overall treatment approach in the younger and/or fitter patient is to achieve remission with an intensive induction course of cytotoxic therapy. Subsequent post-remission treatment, guided by a combination of pretreatment determinants and by the response to initial therapy, generally includes further consolidation courses of cytotoxic therapy. In poorer risk groups, when age, comorbidities and donor availability permit, an allogeneic stem cell transplant (SCT) is also a consideration.

Impact of cytogenetic and molecular abnormalities on diagnosis and prognosis in AML

Chromosomal abnormalities in leukaemic blasts are present in 50–60% of AML cases and stratify prognosis into favourable, intermediate and adverse risk groups. Favourable prognosis subtypes include APL (associated with t(15;17) translocation and PML-RARA rearrangement) and the core binding factor leukaemias (Table 1).

The adverse risk group includes patients with complex karyotypes, aberrations of chromosomes 5 or 7, and a particularly poor risk group with a monosomal karyotype. Patients with adverse risk AML generally have a dismal 5-year survival with chemotherapy alone such that, in appropriate patients, allogeneic SCT is considered once remission is achieved.

The most heterogeneous group is the intermediate risk group in which patients with a normal karyotype (NK-AML) automatically fall. A proportion of these patients will be cured by chemotherapy alone; however, determining which patient is likely to relapse and hence benefit from allogeneic SCT in first remission has not been easily defined. Recently, the discovery of recurrent gene mutations that reflect prognosis within the NK-AML group, has allowed further refinement of AML classification and improved risk stratification7 (Table 1). Three of these mutations, NPM1, CEBPA and FLT3-ITD, are increasingly being utilised to guide management decisions. Thus, NK-AML patients with NPM1 or biallelic CEBPA mutations have a favourable prognosis, akin to the favourable risk group (as defined by karyotype).9

Table 1 Cytogenetic and molecular-genetic risk stratification in AML‡

<table>
<thead>
<tr>
<th>Risk profile</th>
<th>Cytogenetic</th>
<th>Molecular genetic abnormalities further stratifying normal karyotype AML</th>
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<tbody>
<tr>
<td>Favourable</td>
<td>t(15;17)q22</td>
<td>Mutated NPM1 with FLT3-ITD mutation</td>
</tr>
<tr>
<td></td>
<td>Core binding factor leukaemias</td>
<td>Biallelic mutated CEBPA</td>
</tr>
<tr>
<td></td>
<td>t(8;21)q22;q22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1);q22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(16;16)q13.1;q22</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Trisomy 8</td>
<td>FLT3-ITD mutation</td>
</tr>
<tr>
<td></td>
<td>t(9;11)p22;q23</td>
<td></td>
</tr>
<tr>
<td>Adverse</td>
<td>Complex karyotype (&gt;3 abnormalities)</td>
<td>Mutated NPM1 without FLT3-ITD mutation</td>
</tr>
<tr>
<td></td>
<td>Monosomal karyotype†</td>
<td>Biallelic mutated CEBPA</td>
</tr>
<tr>
<td></td>
<td>-5 or del(5q)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-7</td>
<td>Abnormalities of 17p</td>
</tr>
<tr>
<td></td>
<td>11q23 abnormalities</td>
<td>(other than t(9;11) inv(3)(q21;q26.2) t(3;3)(q21;q26.2) t(6;9)(q23;q34)</td>
</tr>
</tbody>
</table>

†Monosomal karyotype is defined as two or more autosomal monosomies or one autosomal monosomy with at least one other structural abnormality. ‡Adapted from European LeukemiaNet Recommendations.7

Patients with FLT3-ITD mutations have a poorer prognosis with some evidence suggesting a benefit from allogeneic SCT in first remission. Other recurrent molecular abnormalities in AML include mutations in c-KIT, IDH1, IDH2, WT1, RUNX1, TET2 and DNMT3A; however, their prognostic impact and utility in guiding management remain to be fully defined.10

Treatment of acute promyelocytic leukaemia

Changes in the management of APL have resulted in one of the most significant advances in acute leukaemia outcomes over the past two decades. Disseminated intravascular coagulation is a major feature of APL, and until recently, the early death rate exceeded 20%, primarily due to intracerebral and pulmonary haemorrhage. With current management regimens, overall survival is approaching 90–95%, especially in those <60 years.11 Refinements in APL therapy include meticulous attention to reversing coagulopathy, with aggressive plasma and platelet support, and a treatment regimen quite
distinct to what is used in other AMLs. APL-specific therapy incorporates all-trans retinoic acid (ATRA), in combination with anthracycline based chemotherapy. In Europe, treatment of high-risk APL patients (white cell count > 10 × 10⁹/L) has involved chemotherapy intensification during consolidation with intermediate or high-dose cytarabine. In contrast, the strategy to reduce the risk of relapse that has gained most popularity in Australia has involved addition of arsenic trioxide during both induction and consolidation.12 Arsenic trioxide is already established as a highly effective agent in the management of relapsed APL,13 and its incorporation into initial therapy has reduced reliance on ‘traditional chemotherapy’. The APL ‘differentiation syndrome’, previously known as the retinoic acid syndrome, is a potentially fatal capillary leak syndrome induced by both ATRA and arsenic.14 Its incidence and severity can be minimised by judicious use of corticosteroids and chemotherapy. Finally, in contrast with non-APL AML, where maintenance has not proven to be effective, post-consolidation oral maintenance therapy has been shown in some studies to decrease further the risk of relapse.15,16

Treatment of AML (non-APL) in patients ≤60 years

Induction chemotherapy with cytarabine for 7 days combined with 3 days of an anthracycline, usually daunorubicin, form the so-called ‘7-3’ regimen that has been the standard of care for several decades and remains widely utilised. Efforts to improve the effectiveness of this combination include alternative anthracyclines (idarubicin, mitoxantrone), intensification of the dose of cytarabine (so-called high-dose ara-C or HiDAC), higher doses of daunorubicin, and the addition of a third drug such as thioguanine or etoposide to the traditional 7-3 backbone.

Sequential randomised Australasian trials have contributed to this field over the past two decades, in particular two approaches to the intensification of the 7-3 induction with the addition of etoposide (the 7-3-7 regimen)17 and a subsequent trial utilising HiDAC in induction (HiDAC-3-7 vs 7-3-7).18 While neither approach improved remission rates, there was significant improvement in the durability of remission in those who responded. A subsequent study replacing daunorubicin with idarubicin in HiDAC-3-7 (the ICE regimen) in induction gave high complete remission rates of 80% although further HiDAC in consolidation (ICE) did not provide additional survival benefit over two consolidation cycles with idarubicin, conventional dose cytarabine and etoposide (‘little’ ICE; 61% vs 62% overall survival at 3 years).19 The potential disadvantage of HiDAC in induction is its increased toxicity and many cooperative groups reserve the use of HiDAC for post-remission therapy where it is has also been shown to improve outcome.7,20

Higher dose daunorubicin (90 mg/m²) has recently been compared to standard dose (45 mg/m²) in younger AML (<60 years)21 and in older AML (>60 years)22 patients in two separate randomised trials. In younger AML improvements in remission rates and overall survival were demonstrated, particularly in those <50 years with the exception of patients with adverse cytogenetics or FLT3-ITD mutation, where no benefit was observed. In the elderly, no increased toxicity was reported with higher dose daunorubicin; however, an overall survival benefit was only noted in the 60–65-year-old subgroup. As yet, there is no evidence that daunorubicin 90 mg/m² is superior to 60 mg/m² or to other anthracyclines (idarubicin).

Following remission induction, further consolidation chemotherapy is usually given although the optimal number of cycles is not defined. This commonly incorporates HiDAC with the 3 g/m² dose shown to be superior in consolidation over 100 mg/m² or 400 mg/m² in patients <60 years old,20 particularly in intermediate or favourable prognosis subgroups.23

Treatment of AML in older patients

One of the areas in greatest need of alternative and improved therapy is the treatment of older adults who comprise the majority of AML patients. Increasing age is a poor prognostic marker in all AML subgroups, partly due to poorer tolerance of cytotoxic therapy, but also to innate properties of the leukaemia, with more complex karyotypes and monosomies of chromosome 5 and 7 and more AML arising secondary to an underlying myelodysplastic syndrome (MDS) or prior cancer treatments. Traditionally, there has been some reluctance to employ intensive induction chemotherapy in older patients due to concerns regarding toxicity and poor response rates. However, in appropriately selected patients, early death rates are actually lower with intensive induction compared to supportive care or low-dose chemotherapy approaches. In a Swedish Acute Leukaemia Registry study, intensive induction chemotherapy given to elderly AML patients with a good performance status resulted in complete remission (CR) in 65% of 60–69-year-olds and 50% of 70–79-year-olds.24 While the majority of these patients ultimately relapse, attaining a CR provides a period of time with less hospital visits and better quality of life.
Agents targeting epigenetic mechanisms such as the DNA hypomethylating drugs azacitidine and decitabine show some promise in elderly AML. In a phase III study of azacitidine compared with conventional care regimens in high-risk MDS and low blast count AML (20–30% marrow blasts), the AML subset showed an improved median overall survival of 24.5 months compared to 16 months in the conventional care arm.25 Decitabine has also been reported to improve response rates and possibly overall survival in de novo and secondary elderly AML compared to conventional regimens.26

**Targeted therapies in AML**

Targeted inhibition of constitutionally activated FLT3 and other tyrosine kinases has been made possible by the development of several tyrosine kinase inhibitors (TKI). Clinical trials combining FLT3 inhibitors with traditional chemotherapy with the aim of improving outcome in AML with FLT3-ITD mutations have had mixed results.27 This approach is the basis of the upcoming phase III Australasian Leukaemia and Lymphoma Group trial in adult AML (AML M16).

**Acute lymphoblastic leukaemia**

In the WHO classification, ALL subtypes are defined primarily on the basis of immunophenotype and recurrent cytogenetic and molecular abnormalities2 (Table 2). The major subgroups include the precursor B and T lymphoblastic leukaemias. A rapidly proliferative mature B-cell neoplasm, Burkitt lymphoma, can also present as an acute leukaemia, but is generally treated differently to ALL. While ALL is the most common malignancy of childhood there is a second incidence peak after 50 years of age. In Australia the incidence of ALL is 1.5/100 000.6

**Prognostic factors in ALL**

Historically, age and white cell count have been the most important prognostic factors in both childhood and adult ALL. Depending on the protocol, the age cutoff for ‘high-risk’ ranges anywhere from 35 to 60 years, and initial white cell counts from 5–30 ¥ 10⁹/L.29 Males historically have had slightly worse survival, although this difference has diminished recently. Cytogenetic and molecular abnormalities provide prognostic information and can be targets for therapy. The most frequent structural cytogenetic abnormality in adult ALL (15% to 30%) is the Philadelphia (Ph) chromosome (t(9;22)(q34;q11)) resulting in the BCR-ABL fusion gene. Up until recently, patients with Ph-positive ALL had a dismal prognosis with little chance of a cure outside of allogeneic SCT. With the advent of specific TKI used in combination with chemotherapy, treatment results are improving although allogeneic SCT is still usually recommended in suitable patients with a well-matched donor. The efficacy of imatinib and chemotherapy is well established,30,31 and there is now emerging evidence supporting the use of the newer more potent TKI, especially dasatinib, which has greater CNS penetration.32

Building on the success of paediatric practice, the monitoring of minimal residual disease (MRD) after induction and during consolidation has become another powerful predictor of disease recurrence and is used in current trials to stratify standard-risk patients. This approach is based upon the observations that early response reflects the effectiveness of the treatment regimen, host pharmacodynamics and pharmacogenetics, and treatment adherence. MRD detection assays utilise either flow cytometry to detect an aberrant immunophenotype specific for the leukaemic clone, or polymerase chain reaction-based detection of a fusion

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**Table 2** WHO classification of acute lymphoid leukaemias2

| Precursor lymphoid neoplasms (acute lymphoblastic leukaemias) |
| B lymphoblastic leukaemia not otherwise specified |
| B lymphoblastic leukaemia with recurrent genetic abnormalities |
| t(9;22)(q34;q11.2) (Philadelphia chromosome/BCR-ABL fusion gene) |
| t(11;19)(q23;p13.3) |
| t(12;21)(p13;q22) |
| t(5;14)(q31;q32) |
| hypodiploid |
| hyperdiploid |

| T lymphoblastic leukaemia† |
| Mature B-cell neoplasms |
| Burkitt lymphoma presenting as an acute leukaemia |

†Common genetic abnormalities seen in T-ALL include rearrangements with T-cell receptor loci resulting in altered transcription factor gene expression, rearrangements of TAL1 and mutations of NOTCH1 and hCDC4 genes.
transcript, gene mutation or monoclonal immunoglobulin or T-cell receptor rearrangement. Although adults have higher post-induction MRD levels compared to children, monitoring of MRD is also informative in adults.31

Chemotherapy strategies: induction, post-induction intensification, CNS prophylaxis maintenance

Initial CR rates are high and are achieved in approximately 98% of children and up to 85% of adults.34 The mainstays of induction therapy are vincristine, anthracyclines, corticosteroids and L-asparaginase although the latter is perhaps underused in adults due to poorer tolerance. In children, there is convincing evidence for the inclusion of L-asparaginase during induction and the post-remission phases. The situation in adults is less clear, however, as the absence of L-asparaginase from one of the commonly used regimens (hyper-CVAD) does not appear to have an adverse impact on survival.34 The availability of pegylated asparaginase has improved tolerance in adults with a longer serum half-life and a reduced risk of hypersensitivity.

The post-remission phase (consolidation or intensification) usually involves a complex series of cytotoxic treatments including cytarabine, high-dose intravenous methotrexate and cyclophosphamide. The general principle, that significant post-induction intensification improves outcomes, appears to hold true across treatment studies in children. However, there are concerns that this may not be the case in adults due to higher rates of toxicities and ‘reduced’ compliance. The use of MRD to stratify patients towards more or less intensive treatment will potentially avoid these toxicities in selected patients.

Two other key features of adult ALL management are the use of CNS prophylaxis and prolonged maintenance chemotherapy. Without CNS prophylaxis, the rates of CNS relapse are 30–50%.35 The incorporation of specific measures such as cranial irradiation, intrathecal chemotherapy and systemic chemotherapy regimens that include agents with CNS penetration, such as dexamethasone, high-dose methotrexate and high-dose cytarabine has been demonstrated to markedly reduce this complication.36 While cranial irradiation is still included in some protocols, there has been a developing trend for it to be supplanted by drug-based regimens because of the radiotherapy-associated morbidity of acute neurotoxicity and long-term neurocognitive deficits. Maintenance therapy is a unique feature of ALL treatment and consists of 2 to 3 years of post-consolidation therapy, usually administered orally with antimetabolites. A commonly Oused maintenance regimen is oral weekly methotrexate and daily mercaptopurine, although other regimens include thioguanine, dexamethasone and vincristine.29

What have we learnt from paediatric protocols in treating adolescents and young adults (AYA)

It has recently been recognised that adolescents and young adults who are treated on so-called ‘adult protocols’ fare significantly worse than the same age groups treated on ‘paediatric protocols’.37 The precise explanation for this observation has not fully been elucidated although variations in protocols and in physicians’ approaches to treatment may contribute. Paediatric protocols tend to use higher cumulative doses of glucocorticoids, vincristine and L-asparaginase, whereas adult regimens rely more on anthracyclines and alkylating agents.37,38 AYA patients who are seen by adult haematologists are more likely to be living independently than those seen by paediatricians, and thus face more challenges with protocol compliance.

Treatment of older patients with ALL

Elderly patients, commonly defined as greater than 60 years, have a worse prognosis than younger patients with long-term survival being less than 20%. Unfortunately, this has not changed significantly over the last 20 years and few patients are being enrolled in prospective trials. Elderly patients with Ph+ ALL are usually treated with a TKI, vincristine, steroids and possibly reduced dose anthracycline although the GIMEMA group demonstrated that imatinib plus steroids without any chemotherapy was very well tolerated with a 100% CR rate and a 20-month median survival.39

Role of allogeneic stem cell transplantation in acute leukaemia

Allogeneic SCT is a potentially curative therapy for patients with acute leukaemia with the benefit derived in part from the chemotherapy and/or radiation in the preparative regimen in conjunction with an immunologically mediated graft versus leukaemia effect. In both AML and ALL allotransplantation is often recommended in first remission in patients with adverse prognostic features when the relapse risk is high and justifies exposure to the potential toxicity of SCT. Another frequent scenario is in second remission following relapse as these patients are rarely cured with conventional chemotherapy. With advances in allogeneic SCT the trade-off of toxicity-for-cure is lessening and we are able to broaden the types of patients (including older patients) who are

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suitable for SCT. These advances include (i) better identification of those likely to benefit from an earlier transplant such as NK-AML patients with adverse molecular markers; (ii) better selection of unrelated donors with the use of high-resolution allele level human leukocyte antigen typing; (iii) the use of umbilical cord blood as a stem cell source; (iv) reduced intensity conditioning (RIC) regimens; and (v) advances in supportive care. RIC is potentially attractive for the older patient in whom the outcome of allogeneic SCT has been poor due to high treatment-related mortality.40

In ALL, allogeneic SCT clearly benefits several subgroups of patients, such as Ph+ ALL (even when treated with a TKI), those with a poor initial response to treatment, and adults with MLL gene rearrangements (e.g. t(4;11)). However, the selection of patients and the timing of allogeneic SCT in ALL remain controversial. A recently published large multicentre trial concluded that even standard-risk patients in first complete remission benefit more from allogeneic SCT than from chemotherapy.31 This conclusion contrasts with that of previously published studies in which allogeneic SCT has not favoured standard-risk patients. Perhaps these apparently conflicting results can be explained by improvements in transplantation as well as variability in the definitions of standard and high risk between these studies.

Future directions

Aided by the increasing accessibility and affordability of high throughput molecular techniques the identification of genetic and epigenetic abnormalities in acute leukaemia is advancing rapidly. This knowledge not only furthers our understanding of the pathogenesis of leukaemia but provides potential therapeutic targets that will shape our future treatment strategies.


41 Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood* 2008; 111: 1827–33.
**Abstract**

**Background:** *Blastocystis* is a common, enteric parasite. The pathogenicity of the organism is uncertain, but subtypes (ST) 1 and 3 have been reported more likely to cause irritable bowel-like symptoms.

**Aims:** We treated symptomatic patients positive for *Blastocystis* with conventional therapy and analysed 16 small-subunit (SSU) rDNA to assess clearance and carriage rates and ST prevalence of the parasite in the asymptomatic household members.

**Methods:** In a longitudinal, prospective case study, 11 symptomatic patients positive for *Blastocystis* underwent outpatient clinical assessment to exclude other diagnoses before 14 days of either metronidazole 400 mg three times daily or trimethoprim/sulfamethoxazole 160/800 mg twice-daily therapy. Faecal specimens were collected from patients at baseline, day 15, 28 and 56 after therapy and from 17 family members and eight pets at day 15. Specimens were analysed using faecal smear, culture and polymerase chain reaction analysis of 16SSU rDNA.

**Results:** No patient cleared the organism following therapy. ST 1 (45%), 3 (36%), 4 (36%) and 6 (9%) were found in the symptomatic *Blastocystis* patients, and ST identified before and after therapy were identical in each individual. All household contacts were positive for *Blastocystis* and 16/17 (94%) contacts showed identical *Blastocystis* ST to the symptomatic family member. All pets were positive for *Blastocystis* with polymerase chain reaction testing, 7/8 (88%) demonstrating ST concordance with the symptomatic *Blastocystis* patients.

**Conclusions:** Conventional therapy is ineffective for symptomatic *Blastocystis* infection. The high prevalence of *Blastocystis* infection within households suggested transmission between humans and their pets. Subtyping analysis of SSU rDNA alone in *Blastocystis* does not appear to predict pathogenicity.

**Introduction**

*Blastocystis* are ubiquitous, anaerobic parasites commonly identified in human and animal stool. Reports suggest that *Blastocystis* causes disease in humans. Symptoms attributed to the organism are abdominal pain, bloating and diarrhoea. The genus of *Blastocystis* comprises at least 13 subtypes (ST) that demonstrate moderate animal species specificity. There is regional variation in the prevalence of different *Blastocystis* ST found in humans, although ST3 is universally the most common. Recent studies have suggested that ST1 and/or ST3 may be more likely to be pathogenic in humans. The parasite cyst is transmitted by the faecal–oral route, and close contact with animals may be a risk factor for acquisition of infection.

Metronidazole, the most commonly prescribed drug for *Blastocystis*, is reported to have widely varying rates of efficacy. These inconsistencies may be attributed to insensitive diagnostic methods, variability of *Blastocystis* ST response to drugs, rapid reinfection or drug resistance.

In this pilot study, we examined the *Blastocystis* ST of symptomatic patients and their respective human and animal household contacts (HC) and recorded the
efficacy of conventional therapy in the patients. We aimed to evaluate antimicrobial efficacy, the rate of environmental reinfection, and explore ST variations in clinical presentation or response to therapy.

Methods

Study outline

This prospective longitudinal study was conducted in a rural specialist outpatient clinic (Toowoomba Gastroenterology Clinic). Patients who presented complaining of chronic gastrointestinal symptoms and were positive for Blastocystis carriage were screened to exclude other causes for symptoms. Faecal samples were collected from eligible patients before and after a course of antimicrobial therapy for Blastocystis, and at completion of the antimicrobials, faecal samples were collected from all the human and animal HC.

Inclusion protocol

Thirteen adult patients presenting consecutively to the clinic from 09/04/2008 to 31/08/2009 positive for Blastocystis carriage and complaining of gastrointestinal symptoms of more than 6 weeks duration were assessed clinically. Blood tests, full blood count, serum calcium, thyroid function tests and tissue transglutaminase antibody were checked. Faecal microscopy, culture and toxin assay for Clostridium difficile was performed to check for ova, cysts, oocysts and bacterial pathogens. In addition, a faecal ELISA kit (‘ProsSpecT, Remel Xpect’ by Oxoid, Cambridge, UK) tested for Giardia and Cryptosporidium. A validated, in-house real-time faecal polymerase chain reaction (PCR) analyses carried out by Statens Serum Institute laboratory excluded occult Dientamoeba fragilis, Giardia duodenalis, Cryptosporidium spp., Entamoeba histolytica and E. dispar infection. A 3-day culture for hookworm was performed. Helicobacter pylori infection was evaluated by gastric biopsy at endoscopy. One patient with ulcerative colitis and another patient unable to undergo endoscopy were excluded from the study.

The remaining 11 symptomatic Blastocystis patients (SBP) proceeded to upper, lower endoscopy and capsule enteroscopy, performed by the same endoscopist. Mucosal biopsies were taken from the gastric antrum and duodenum for histology and estimation of disaccharidase levels. Biopsy specimens were taken from the ileum, right and left sides of the colon.

Study protocol

Three baseline faecal specimens were taken from 11 eligible SBP prior to starting 14 days of metronidazole 400 mg three times daily or trimethoprim-sulfamethoxazole 160 mg/800 mg twice daily. Further faecal samples were taken within 48 h of ceasing antibiotics and 2 and 6 weeks after cessation of therapy.

Trimethoprim-sulfamethoxazole 160 mg/800 mg twice daily for 14 days was given to patients who had previously failed one course of the identical dose of metronidazole or who were intolerant of the medication. Patients were reviewed clinically initially 2 weeks prior to therapy, at the completion of the antibiotic therapy and 6 weeks later at the completion of the study. All patients kept a diary recording the number of daily bowel movements and general well-being (scored 1–10; from poor to excellent). They also recorded whether any HC or animal was experiencing any change in gastrointestinal health.

All the HC of these patients were asked to provide fresh stool specimens within 48 h of the symptomatic patient finishing the course of therapy. Stool specimens were also collected on this date from all the animal HC. All SBP stool specimens were subjected to routine pathology faecal specimen microscopy and culture throughout the study. All stool specimens (SBP, HC and animal HC) were subject to smear, culture and PCR for detection of Blastocystis and subtyping.

Diagnostic methods

All samples were run in parallel for the presence of Blastocystis using a simple fresh unstained wet faecal smear, in vitro culture and PCR (confirmed as Blastocystis using DNA sequencing). An individual human or animal was considered positive for Blastocystis if any one of the tests was positive.

Parasitological methods

Fresh unpreserved faecal samples from patients were divided into two samples upon receipt. One sample was screened using a faecal smear by a commercial diagnostic laboratory in Brisbane while the other was transported to the School of Veterinary Science, University of Queensland (SVS-UQ). Unstained fresh faecal smears were examined under ×40 magnification by light microscopy. The load of Blastocystis organisms was classified as light, medium or heavy (<5, 5–10 and >10 organisms per high-powered field (O/HPF)).

Additionally, 100 mg of stool was inoculated in Jones’ culture medium17 and incubated at 37°C for 48–72 h. Cultures were examined for the presence of Blastocystis by light microscopy.

Molecular methods

DNA was extracted from unpreserved faecal samples and pelleted cultures of Blastocystis using the QIAamp DNA
S10 O/HPF in five specimens from all patients, household members and animals were subjected to PCR analyses. Three different published PCR capable of amplifying the small-subunit (SSU) rRNA gene of ST 1–13 of Blastocystis18–21 were used to maximise the likelihood of detecting mixed ST infections.

All PCR products positive for Blastocystis were subjected to DNA sequencing and phylogenetical analysis to identify the ST. PCR products were run on gels of 1.5% agarose in 1× Tris-acetate-EDTA buffer at 150V in a Biorad electrophoresis system and were purificed using Purelink PCR Purification Kit (Invitrogen, Grand Island, NY, USA) prior to sequencing. Sequencing was done using an ABI 3130xl Genetic Analyzer (Applied Biosystems, Mulgrave, Vic., Australia) using a Ready Reaction Kit Version 3.1 (PE Applied Biosystems, Foster City, CA, USA) and sequences edited and assembled using Finch TV v 1.4.0 DNA (Geospiza Inc., Seattle, WA, USA).

Sequences were deemed as ‘mixed’ when sequence profiles were characterised by a clean sequence with multiple peaks at sites of nucleotide polymorphism.

DNA sequences were aligned with 15 previously sequenced Blastocystis SSU rRNA genes sourced from GeneBank (National Center for Biotechnology Information) representing the 13 established ST described from mammals and birds. Distance-based analyses were conducted on readable sequences using Kimura 2-parameter distance estimates, and trees were constructed using the neighbour-joining algorithm using Mega 3.122 software (The Biodesign Institute, Tempe, AZ, USA). Proteromonas lacreate (U37108) was used as an out-group. Bootstrap analyses were conducted using 1000 replicates.

Ethics approval
The study was approved by The University of Queensland Medical Research Ethics Committee and Animal Ethics Committee and registered with the Australian New Zealand Clinical Trials registry (http://www.ANZCTR.org.au) ACTRN:12610001066077.

Results
Clinical characteristics of patients and household members
Male (n = 3) and female (n = 8) patients with an age range of 23–71 years participated in the study. The shortest symptom duration was 3 months in one patient, six patients had exhibited symptoms for 2 years and the other five patients had complained of symptoms for more than 10 years. Presenting clinical symptoms were bloating (7/11; 64%), diarrhoea (5/11; 45%), nausea (5/11; 45%), flatulence (4/11; 36%), variable bowel habit (4/11; 36%), abdominal pain (3/11; 27%) and fatigue (2/11; 18%; Table 1).

Five patients had previously received therapy for Blastocystis, which did not clear either the infection or their symptoms. The remaining patients were naïve to therapy. During the period of the study, no SBP had any organism other than the Blastocystis noted in the faecal testing. No patient demonstrated eosinophilia on the peripheral full blood film. In total 17 HC submitted specimens, only one teenage HC was unable to donate a sample (three other HC specimens collected from that family). Eight animal HC samples were collected, five dogs and three cats from seven households (one of two dogs in one household escaped submitting a specimen). Household water sources were varied. No HC or animal HC was undergoing medical investigation or therapy for gastrointestinal symptoms.

Endoscopy
All patients displayed normal stomach and duodenum, and all were negative for Helicobacter pylori at gastric biopsy. Duodenal biopsy showed mild intra-epithelial lymphocytosis in 2/11 (SBP2 and 4) patients (Table 1). Colonoscopy with ileoscopy was macroscopically normal in 8/11 patients. One patient (SBP1) displayed prominent lymphoid follicles in the terminal ileum, confirmed on ileal biopsy. All the other ileal mucosal biopsies were normal. Random colonic mucosal biopsies were normal in 10/11 patients; SBP2 had mild focal active colitis noted at histology only. Capsule endoscopy looked normal in nine patients; two patients (SBP1 and 7) displayed prominent distal ileal lymphoid follicles.

Therapy
Eight patients were prescribed metronidazole, and one patient (SBP7) complained of severe nausea but completed the course. Three patients (SBP2, 4 and 9) were prescribed trimethoprim/sulfamethoxazole, and one patient (SBP7) developed a rash and ceased the tablets on day 11 of the 14-day course.

Faecal smears and culture in patients
Faecal smear results prior to the commencement of treatment demonstrated a parasite load of <5 O/HPF in five
<table>
<thead>
<tr>
<th>Patient</th>
<th>Main symptoms</th>
<th>Duration of symptoms</th>
<th>Previous therapy treated before inclusion in study</th>
<th>Reversible causes treated before inclusion in study</th>
<th>Small bowel and colonic endoscopy</th>
<th>Baseline week median daily BO/WB</th>
<th>Week 6 daily median BO/WB</th>
<th>ST at baseline</th>
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<tbody>
<tr>
<td>1</td>
<td>Pain</td>
<td>10 years</td>
<td>Yes, ×2 2 years ago</td>
<td>Giardia</td>
<td>Prominent lymphoid follicles TI</td>
<td>1/8</td>
<td>1/8</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Bloating</td>
<td>11 years</td>
<td>Yes, ×2 5 years ago</td>
<td>Enterobius vermicularis</td>
<td>Mild focal active colitis colonic biopsy</td>
<td>3/8</td>
<td>4/8</td>
<td>3</td>
</tr>
<tr>
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<td>Alternating BH</td>
<td>2 years</td>
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<td>Nil</td>
<td>N</td>
<td>1/10</td>
<td>1/9</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Nausea</td>
<td>2 years</td>
<td>Yes, ×3 1 year ago</td>
<td>Aeromonas low lactase</td>
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<td>3/8</td>
<td>3/8</td>
<td>3</td>
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<td>5</td>
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<td>2 years</td>
<td>No</td>
<td>Nil</td>
<td>Colonic polyp</td>
<td>2/9</td>
<td>2/8</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>Nausea</td>
<td>3 months</td>
<td>No</td>
<td>Nil</td>
<td>2mm nodule mid-small bowel</td>
<td>1/7</td>
<td>1/7</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>Fatigue</td>
<td>2 years</td>
<td>No</td>
<td>Nil</td>
<td>Prominent lymphoid follicles TI</td>
<td>1/7</td>
<td>1/8</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Bloating</td>
<td>10 years</td>
<td>Yes, ×3 10 years ago</td>
<td>Nil</td>
<td>N</td>
<td>1/9</td>
<td>1/9</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Nausea</td>
<td>2 years</td>
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<td>Nil</td>
<td>N</td>
<td>2/6</td>
<td>1/8</td>
<td>1</td>
</tr>
<tr>
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<td>30 years</td>
<td>No</td>
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<td>1/7</td>
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<td>1</td>
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<td>N</td>
<td>N</td>
<td>2/7</td>
<td>1/7</td>
<td>4 + 6</td>
</tr>
</tbody>
</table>

BH, bowel habit; BO, Bowel actions per day; TI, terminal ileum; WB, general well-being, 10/10 excellent.
patients and > 5 O/HPF in the remaining patients. All faecal smears or cultures performed at SVS-UQ were positive for *Blastocystis* at days 14, 28 and 56 (Table 2).

Faecal smears performed at the commercial laboratory showed negative results in 4/11 (36%), 2/11 (18%) and 3/9 (33%) at 14, 28 and 56 days, respectively. In 3/33 specimens examined at SVS-UQ, the faecal smear result was negative, and the culture was positive (SBP6 at 28 days; SBP8 at 28 and 56 days). Change in parasite excretion load pre- and post-therapy was variable within the study group (Table 2). Four SBP (SBP6, 7, 9 and 10) had ‘occasional leukocytes’ noted in less than 50% of each individual’s faecal microscopy specimens; all other specimens were negative for faecal leukocytes.

**PCR and genetic subtyping of Blastocystis in patients**

All patients were PCR positive for *Blastocystis* after antibiotic therapy. Subtyping of *Blastocystis* showed that all patients retained the same ST following therapy with antibiotics. Three patients (SBP 4, 9 and 11) were found to have mixed ST infections, and two of these patients appeared to acquire the second ST after therapy. The ST identified in the patients were ST1 (5/11; 45%), ST3 (4/11; 36%), ST4 (4/11; 36%) and ST6 (1/11; 9%; Table 3).

**Faecal smears, cultures and PCR subtyping in HC**

Seventeen HC were tested, and 10/17 (59%) contacts were positive for *Blastocystis* on faecal smear. *Blastocystis* organisms were low in number, and only 1/10 positive specimens contained >5 O/HPF. Cultures were positive in 5/17 animal HC (29%). However, PCR analysis of these specimens showed that 17/17 (100%) of HC had evidence of *Blastocystis* carriage. Readable DNA sequences allowed ST determination in all except one household member (SBP11/HC1). The patients and their HC had concordant *Blastocystis* ST in 10/11 patients. SBP8 was the only patient to have a different ST to the HC (Table 4).

**Faecal smears, cultures and PCR subtyping in animal contact**

Seven households had contact with eight household animals. Only 2/8 (25%) animals were positive for *Blastocystis* on faecal smear, and none was positive on

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**Table 2** *Blastocystis* faecal smear and culture results in patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>0 days</th>
<th>14 days</th>
<th>28 days</th>
<th>56 days</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>UQ smear</td>
<td>CL+</td>
<td>UQ smear</td>
<td>CL+</td>
</tr>
<tr>
<td>1</td>
<td>&gt;5 MTZ+</td>
<td>+</td>
<td>&gt;5 +</td>
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</tr>
<tr>
<td>2</td>
<td>&gt;5 TS-</td>
<td>-</td>
<td>&gt;5 +</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>&gt;5 MTZ+</td>
<td>+</td>
<td>&lt;5 +</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>&gt;10 TS+</td>
<td>+</td>
<td>&lt;5 +</td>
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<tr>
<td>5</td>
<td>&gt;10 MTZ+</td>
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<td>&lt;5 +</td>
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<tr>
<td>6</td>
<td>&lt;5 MTZ+</td>
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<td>&lt;5 +</td>
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<tr>
<td>7</td>
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<tr>
<td>11</td>
<td>&lt;5 MTZ+</td>
<td>+</td>
<td>&lt;5 +</td>
<td>+</td>
</tr>
</tbody>
</table>

Faecal smear results: organisms per high-powered field light microscopy x40 magnification: <5, >5 and >10. Smear, number of *Blastocystis* organisms per high-powered field in wet faecal smear; time: 0 days, before antibiotic therapy 14 days, within 48 h of finishing antibiotic therapy. CL, commercial laboratory; MTZ, metronidazole; n/a, not available; TS, trimethoprim/sulfamethoxazole; UQ, University of Queensland laboratory.

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**Table 3** *Blastocystis* subtype results in symptomatic patients pre- and post-therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Subtype before therapy</th>
<th>Subtype after therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
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</tr>
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<td>3</td>
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<td>4</td>
<td>3</td>
<td>3+4</td>
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</tr>
<tr>
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<td>1</td>
<td>1+4</td>
</tr>
<tr>
<td>10</td>
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<td>1</td>
</tr>
<tr>
<td>11</td>
<td>4+6</td>
<td>4+6</td>
</tr>
</tbody>
</table>
culture. However, all eight animals had positive PCR tests. All of the animals harboured at least one ST in common with each of the corresponding seven patients. Most animals (7/8) also had ST in common with the corresponding HC (HC11 was the exception; Table 4).

**Clinical follow-up at 6 weeks**

Only one patient reported any change in diary entry (SBP9 reported two–point rise in general well-being at 6 weeks post-therapy; Table 1). No HC or animal was reported to have any change in gastrointestinal health.

**Discussion**

In this study, none of the eleven patients with symptomatic blastocystosis succeeded in clearing infection following a 14-day course of metronidazole or trimethoprim/sulfamethoxazole. Faecal *Blastocystis* organisms have been detected 2 days after oral ingestion of cysts in mice. Persistence of the parasite within 48 h of ceasing antibiotics in this study suggests failure to clear the parasite and not reinfection. Reported rates of eradication of *Blastocystis* using these antibiotics vary widely in the literature from 22% to 100%. High false-negative rates of *Blastocystis* detection using routine faecal smears have previously been reported, and false negative rates of 50% were confirmed in this study. Light microscopy is an unreliable tool for detecting this polymorphic parasite that exhibits highly variable daily faecal excretion rates.

The vacuolated form, which is the most readily identified form in the faecal smear, may have a 10-fold variation in size, and small vacuolated forms, amoeboid or cystic forms (2–5 μm) with low excretion rates may not be readily identified. Large clinical trials using more sensitive diagnostic tests such as PCR in addition to conventional methods will be required to evaluate accurately the in vivo efficacy of the numerous agents that have been reported to be useful in treating *Blastocystis* and to evaluate new antimicrobials.

The possible causes of antimicrobial failure in clinical *Blastocystis* patients are numerous. Metronidazole and trimethoprim have been studied in vitro, and, although both drugs inhibit growth of *Blastocystis*, higher doses are needed to be cytotoxic. Delivery of a cytotoxic dose of the antimicrobial to the organism in vivo may be problematic. Both antibiotics are rapidly absorbed systemically, primarily in the small bowel (70% of a single oral dose of both agents is excreted in urine), and little active drug reaches the colon. In animal studies, *Blastocystis* has been found primarily in the caecum and proximal colon. Endoscopic reports in humans demonstrate viable *Blastocystis* organisms in caecal fluid and in biopsy specimens of the large bowel mucosa, but in humans, generally, the organism is not invasive. Studies in humans do not report *Blastocystis* in the stomach or duodenum, and no abnormality of the small bowel was noted in this study. It is likely that drugs effective against *Blastocystis* will need to be delivered in high concentration to the lumen of the caecum.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient subtypes</th>
<th>Household contact</th>
<th>Household faecal smear</th>
<th>Household faecal culture</th>
<th>Household PCR subtypes</th>
<th>Animal contact</th>
<th>Animal faecal smear</th>
<th>Animal faecal culture</th>
<th>Animal PCR subtypes</th>
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<td>+</td>
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</table>

PCR, polymerase chain reaction.
Blastocystis ST may also vary in their susceptibility to various antimicrobial agents. Blastocystis ST have shown to differ in their morphology and growth rates,12,35 and a recent in vitro study has reported variation in metronidazole sensitivity between different ST in in vitro culture.36 Studies assessing drug sensitivities may need to take account of the ST and regional origin of the organism.

The pathogenicity of Blastocystis is uncertain. Blastocystis is commonly found in the stools of healthy people, which is in agreement with observations of healthy, yet positive household members in this study. The prevalence in an asymptomatic population in Australia has been reported to be 6%,17 assessed with stained faecal smears, but is reported to be as high as 20–30% in other nations51–53 when using faecal culture and DNA detection tools. However, the existence of healthy carriers does not necessarily exclude pathogenicity. Common parasitic pathogens, such as G. duodenalis and E. histolytica, are known to cause symptomatic disease in less than 50% of infected people.54 Studies have found Blastocystis more commonly in the stools of patients with irritable bowel syndrome,43 and Blastocystis has been linked to outbreaks of diarrhoea in travellers and soldiers in camp.15,41 Most large studies of SBP describe a non-inflammatory watery diarrhoea with no mucosal ulceration or invasion.34,41 This study is the first to examine the small bowel in Blastocystis infection, as previous studies have not reported inspecting the terminal ileum at lower endoscopy.34,42,43 Prominent lymphoid tissue in the terminal ileum was the only mucosal abnormality seen in a minority of patients.

One explanation for the apparent clinical paradox of symptomatic and asymptomatic infected household members may be that ST of Blastocystis vary in their pathogenicity, notably ST312 and ST16–11 have been reported more frequently in symptomatic patients. Other studies have not confirmed any significant difference in the distribution of particular ST between symptomatic and asymptomatic Blastocystis carriers or specific diseases.54–62 Although ST1, rather than ST3, was the most common in our small study, we found no evidence that a particular 16SSU rDNA ST of Blastocystis was more likely to be associated with symptoms. If particular Blastocystis strains are pathogenic, then the differences in the organism may not be apparent with our current subtyping tools directed at rDNA of the dominant faecal strain, or it may be that individual host/parasite interaction determines pathogenicity.

The parasite load may also be a significant factor in causing disease, and no reliable guide to quantification exists. Although previous studies have suggested that Blastocystis infection is considered more severe if five or more O/HPF are recovered on faecal smear, this measure could be unreliable considering the wide variation in daily excretion of the parasite.27 In this study, human and animal HC had fewer parasites positively documented on smear and a lower rate of successful culture of Blastocystis. Many aspects of the life cycle of Blastocystis are unknown. At present, it seems likely that only the thick-walled cyst, which survives water chlorination,49 transmits infection.63 In this study, the universal carriage of Blastocystis in HC and the concordance of subtypes suggest that Blastocystis is easily transmitted. A recent study has also reported concordance of ST between pets and their owners.56 Even if the primary infection is not acquired from the household animal, these animals are likely to remain a reservoir for reinfection.

**Conclusion**

The universal failure of single antimicrobials in this pilot study suggests that future studies may need to investigate efficacy of combinations of antimicrobial therapy as well as clearance rates in different patient subgroups (such as length of time of acquisition of infection or diarrhoea predominant illness). The high concordance of Blastocystis subtypes within households warrants further investigation in a larger study using more specific molecular tools to allow definitive comments on routes of transmission.

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Spontaneous conversion of first onset atrial fibrillation  
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Abstract

Background/Aim: We studied all patients admitted to hospital with first onset atrial fibrillation (AF) to determine the probability of spontaneous conversion to sinus rhythm and to identify factors predictive of such a conversion.

Methods: We retrospectively reviewed charts of 438 consecutive patients admitted to hospital with first onset AF from 1 January 2006 to 31 December 2009. The patients were divided into two groups, recent onset AF defined as AF < 48 h or longer lasting AF, defined as AF > 48 h.

Results: Spontaneous conversion occurred in 54% (n = 203; 95% confidence interval: 49–59%). In the group with first onset AF < 48 h, spontaneous conversion occurred in 77%, compared with 36% in the group with first onset AF > 48 h. Logistic regression analysis identified duration of AF as a highly significant predictor of spontaneous conversion to sinus rhythm (odds ratio 5.9; 95% confidence interval: 4.0–8.6, P < 0.001).

Conclusions: Spontaneous conversion occurred in 54%, increasing to 77% when AF had persisted less than 48 h.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and affects 1–2% of the population, the prevalence increasing with age.1 Approximately 20% of all strokes are attributed to AF.2 Symptoms include palpitations, dyspnoea and haemodynamic distress,3 causing hospitalisations and reducing quality of life.4 If the duration of AF is < 48 h, early cardioversion is often pursued even though the evidence for early rhythm control therapy is lacking.5

Both electrical and pharmacological cardioversion are expensive6 and associated with a rare but potentially life-threatening risk caused by thromboembolic events and ventricular arrhythmias.7,8

Approximately 50% of patients presenting with AF will have spontaneous conversion to sinus rhythm.5,6 AF often begins with short and asymptomatic episodes progressing to more frequent and sustained forms.9 This suggests that the likelihood of spontaneous conversion...
could be higher for patients with first onset AF. To our knowledge no data have been reported on this subject.

We studied all patients admitted to hospital with first onset AF to determine the likelihood of spontaneous conversion to sinus rhythm and to identify factors predictive of such a conversion.

**Methods**

We retrospectively reviewed hospital charts of all patients admitted to Esbjerg Hospital from 1 January 2006 to 31 December 2009 with AF. A total of 1107 patients with AF was hospitalised during this 4-year period.

All charts were reviewed by two of the authors. All patients with a history of AF (731) were excluded. Cases with duration of AF < 5 min were not included (e.g. observed on an electrocardiogram (ECG) monitor). There were 374 patients who met entry criteria, and the following data from their hospital charts were retrieved: age, gender, systemic disorders related to AF (hypertension, diabetes, prior stroke or transient ischaemic attack, ischaemic heart disease, pulmonary embolus, hyperthyroidism, infection, pericarditis), cardiovascular medications including beta-adrenergic receptor antagonist, calcium channel blocking agents, digoxin and amiodarone both before and after admission to hospital. Echocardiographic data with evaluation of left ventricular ejection fraction (LVEF) were available in 82% (n = 307).

The patients were divided into two groups: recent onset AF defined as AF < 48 h; or longer lasting AF, defined as AF > 48 h. AF < 48 h was reserved for patients with a definite onset of symptoms < 48 h. If debut of symptoms was unclear, the patients were categorised as longer lasting AF. All cardioversions were documented by 12-lead ECG or by constant ECG-monitor strip. Conversion was defined as spontaneous if cardioversion occurred before 48 h after admission and the patient did not receive active cardioversion (direct current conversion (DC) or administration of anti-arrhythmic drugs such as flecainide, sotalol or amiodarone). Non-spontaneous/no conversion was defined as patients who received anti-arrhythmic drugs, DC or where rate control was preferred and patients were discharged with permanent AF.

Data are presented as mean value ± 1 standard deviation. We constructed a logistic regression analysis using both univariate and multivariate analysis of all the variables to determine the correlation with spontaneous conversion. The only variables excluded were medicine given after admission because of anti-arrhythmic ability (21 patients were treated with amiodarone). Results are reported as hazard ratio and 95% confidence interval (CI). P < 0.05 was considered significant. SPSS for Windows version 18.0 (Chicago, IL, USA) was used.

**Results**

The study included 374 patients with first onset AF. During hospitalisation all patients received medication for ventricular rate control. Baseline characteristics are summarised in Table 1.

Ten per cent (n = 39) were treated with active cardioversion (DC, amiodarone or flecainid) during admission, whereas 23% (n = 85) were discharged with persistent AF and treatment including warfarin with the intention of active cardioversion after 4 weeks of adjusted treatment with INR in the range of 2.0–3.0.

Spontaneous conversion occurred in 54% (n = 203; 95% CI: 49–59%). During admission no thromboembolic complications to spontaneous conversion were observed.

Logistic regression analysis identified duration of AF as a highly significant predictor of spontaneous conversion to sinus rhythm (hazard ratio: 5.9, 95% CI: 4.0–8.6, P < 0.001) (Fig. 1).

Both slightly and severely reduced LVEF reduced the probability of spontaneous conversion (OR = 0.3; P = 0.004 and P = 0.01), whereas there was a tendency to normal LVEF increasing the probability for spontaneous conversion; however, this was not significant (OR = 1.4; P = 0.2).

**Figure 1** Spontaneous conversion stratified according to duration. AF, atrial fibrillation.
Discussion

Overall, we found that in patients with first onset AF spontaneous conversion occurred in 54%, increasing to 77% when AF had been persistent for less than 48 h.

Given this high probability for spontaneous conversion, this subgroup of patients with AF might benefit from different treatment.

The usual strategy in treatment of AF is often rhythm control even though newer data have not shown a reduction of AF related thromboembolic events.10 Except from haemodynamic unstable patients, ventricular rate control is the first step. In patients with AF < 48 h active cardioversion is often done immediately or shortly after hospitalisation by DC or anti-arrhythmic agents. If AF has been persistent for more than 48 h or duration unknown, active cardioversion is done electively after anticoagulation treatment for 3–4 weeks or after a transoesophageal echocardiography.3

Dell’Orfano J et al. found that patients with spontaneous conversion to sinus rhythm had a shorter admission compared with patients with non-spontaneous conversion (2.4 vs 4.7 days P < 0.0001).4

Electrical cardioversion of AF is associated with a small but significant risk of thromboembolic complications caused by the stunning of the left atrial appendage.11 Berger and Schweitzer12 reported 92 (2%) thromboembolic events in a retrospective analysis of 4621 patients undergoing elective electrical cardioversion. It is generally accepted that patients with AF < 48 h can receive electrical cardioversion without anticoagulative therapy; however, in this study, three thromboembolic events occurred in patients with AF < 48 h.

A study of 400 patients undergoing electrical cardioversion in an emergency department reported no thromboembolic events.13 Rhythm control with electrical cardioversion is an accepted treatment strategy for AF < 48 h;15 however, it is uncertain how many patients presenting with AF have had ‘silent’ AF for longer than 48 h, thus increasing their risk for thromboembolic events.

Thus the ability to identify patients with a high probability of spontaneous conversion could reduce the length of admission, cost and active cardioversion associated risks. Active cardioversion could be delayed, and instead ventricular rate control might be the best initial

Table 1 Baseline clinical characteristics of patients with first onset atrial fibrillation, stratified according to spontaneous conversion and non-spontaneous conversion

<table>
<thead>
<tr>
<th></th>
<th>Patients with spontaneous conversion (n = 203)</th>
<th>Patients with non-spontaneous conversion (n = 171)</th>
<th>Hazard ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67 ± 15</td>
<td>69 ± 14</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Female</td>
<td>114 (44%)</td>
<td>117 (39%)</td>
<td>2.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Underlying systemic disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>99</td>
<td>86</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18</td>
<td>22</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>20</td>
<td>10</td>
<td>1.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>3</td>
<td>3</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>3</td>
<td>1</td>
<td>2.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>21</td>
<td>25</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Infection</td>
<td>40</td>
<td>21</td>
<td>1.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td>13</td>
<td>6</td>
<td>1.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Heart rate</td>
<td>132 ± 24</td>
<td>123 ± 28</td>
<td>1.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of atrial fibrillation &lt; 48 h</td>
<td>129</td>
<td>39</td>
<td>5.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>6</td>
<td>16</td>
<td>0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Severely reduced (&lt;45%)</td>
<td>7</td>
<td>20</td>
<td>0.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Slightly reduced (&gt;45%)</td>
<td>139</td>
<td>105</td>
<td>1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Normal</td>
<td>25</td>
<td>29</td>
<td>0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Medicine at presentation</td>
<td>11</td>
<td>14</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Beta-adrenergic receptor antagonist</td>
<td>171</td>
<td>153</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>47</td>
<td>71</td>
<td></td>
<td></td>
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<tr>
<td>Digoxin</td>
<td>21</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>0</td>
<td>21</td>
<td></td>
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</tr>
</tbody>
</table>

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treatment for these patients. It might even be possible to manage these patients as outpatients.

A number of studies of spontaneous conversion has been published, most of them comparing an anti-arrhythmic agent with placebo. No study has focused on first onset AF.

Dell’Orfano et al. investigated the rate of spontaneous conversion and cost of care in a retrospective study of 114 patients admitted with AF and found that 50% had spontaneous conversion.

Similar results were found in the DAAF Multicenter study where the investigators randomised 239 patients with AF < 7 days to either digoxin or placebo. In the placebo group 46% had spontaneous conversion.

In a retrospective study of 242 patients with AF < 72 h, Danias et al. reported a spontaneous conversion rate of 68%. Furthermore they found that duration was the only predictor of spontaneous conversion, not LVEF.

Cotter et al. examined amiodarone versus placebo for cardioversion in 100 patients with AF < 48 h. In the placebo group 64% converted spontaneously.

Geleris et al. investigated the likelihood of spontaneous conversion for AF < 24 h. They found that 71% of 109 patients with AF < 24 h converted spontaneously, and that duration was a predictor of spontaneous conversion, not LVEF.

That spontaneous conversion occurred in 53% of patients with first onset AF and that duration is a significant predictor of spontaneous conversion are in agreement with previous results, as this was found in all studies investigating it. The mechanisms behind this are uncertain, but an electro physical theory is that AF is promoting electro physical conditions favourable for propagation of AF.

The influence of LVEF has been unclear. Two studies found no association between LVEF and spontaneous conversion, whereas Galve et al. found a correlation similar to this study.

Study limitations

In this study several patients with AF < 48 h received active cardioversion shortly after admission to the hospital. It is possible that some of these patients would have had spontaneous conversion, had they not been actively cardioverted. Therefore this study may underestimate the true incidence of spontaneous conversion.

Furthermore, the retrospective nature of this study prevents us from controlling for possible confounders.

Conclusion

Spontaneous conversion to sinus rhythm occurred in 53% of patients with first-onset AF. Duration of AF is a strong predictor of spontaneous conversion, and when duration of AF was less than 48 h, spontaneous conversion occurred in 75%. Thus, in haemodynamic stable patients with first onset AF < 48 h, waiting with active cardioversion may be the best approach.

Early evaluation of LVEF by echocardiography provides further risk stratification, thus identifying a group of patients with a high probability for spontaneous conversion. As no complications to spontaneous conversion were observed, these patients could potentially be managed as outpatients.

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Associations between serum total bilirubin levels and functional dependence in the elderly

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Key words
elderly, functional dependence, serum total bilirubin.

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Abstract

Background: Many studies support the role of bilirubin as a cytoprotector in chronic inflammatory diseases, such as stroke and atherosclerosis.

Aim: To investigate the relationship between serum total bilirubin levels and functional dependence in older adults.

Methods: Data from the National Health and Nutrition Examination Survey (1999–2002) pertaining to 2235 old adults were analysed. All participants had given a household interview, providing information of five major domains on self-reported functional status (activities of daily living, instrumental activities of daily living, leisure and social activities, lower extremity mobility and general physical activities), had completed serum total bilirubin measurement, and a questionnaire regarding personal health. Poor performance was defined as experiencing difficulty with one or more items in a given domain. Functional dependence was defined as having three or more poor performances in the five major domains. Multiple logistic regression was performed together with quartile-based stratified odds ratio (OR) comparison and trend tests.

Results: The OR of functional dependence for each standard deviation increment in the serum total bilirubin level was 0.56 (P = 0.002). After additional adjustment, the inverse association remained essentially unchanged. In quartile-based analysis, participants with higher quartiles of serum total bilirubin tended to have lower ORs of functional dependence. The trends of lower likelihood of functional dependence across increasing quartiles of the serum total bilirubin level were statistically significant (P < 0.05 for all trends).

Conclusions: Higher serum total bilirubin levels were associated with lower likelihood of functional dependence in older adults.
Introduction

Bilirubin, a tetrapyrrole pigment derived from the breakdown of haemoglobin in senescent red blood cells, reflects the rate of haem turnover and the adequacy of hepatic uptake, conjugation and canicular excretion. In recent years, there has been a growing interest in the antioxidant activity of bilirubin. Its presence in serum suppresses the oxidation of lipids and lipoproteins, particularly of low-density lipoprotein cholesterol, and is directly related to the total serum antioxidant capacity in humans. Bilirubin protects cells from a 10 000-fold excess of oxidants through its rapid regeneration by biliverdin reductase. In addition, there is evidence that bilirubin has anti-inflammatory properties, and inhibits tumour necrosis factor-α (TNF-α)-induced upregulation of E-selectin, vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in vitro. Currently, a growing number of studies has shed light on the potential protective effects of bilirubin against oxidative stress-related diseases, including coronary heart disease, stroke, peripheral arterial disease (PAD), carotid artery atherosclerosis and cancer.

Emerging evidence supports the substantial role of inflammation in poor physical performance and the development of disability. In several population-based surveys, reduced physical performance, muscle strength, muscle mass and disability had significant positive correlations with inflammatory biomarkers, including interleukin-1 (IL-1), IL-6 and C-reactive protein (CRP). Furthermore, connections between inflammation and physical activity have been documented. Bilirubin plays a possible protective role in many chronic diseases; however, there is no evidence to date on the causal relationship between the serum total bilirubin level and physical activities.

We hypothesised that the serum total bilirubin level is inversely associated with functional dependence in the elderly. The purpose of the present analysis was to explore the association between the serum total bilirubin level and functional dependence by analysing data from the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2002.

Methods

Study design and participants

The NHANES is a population-based survey designed to collect information on the health and nutrition status of the US household population. The NHANES used a stratified, multistage and cluster-sampling design to obtain a representative sample of the non-institutionalised civilian US population. The NHANES consisted of a detailed home interview and a health examination conducted in a mobile examination centre. The study population consisted of adults aged 20 years and older. Beginning in 1999, NHANES became a continuous annual survey rather than the periodic survey that it had been in the past. The survey data have been released every 2 years after 1999. Detailed survey operations manuals, consent documents, and brochures of NHANES 1999–2002 are available on the NHANES website. This dataset on the NHANES website is accessible for download and analysis without any permission.

We collected two NHANES datasets (1999–2000 and 2001–2002), which included demographic, examination, laboratory, and questionnaire data. All participants aged <60 years of age were excluded from our analysis. Because individuals aged ≥85 years were treated as being 85 years old in the NHANES dataset from 1999 to 2002, we only enrolled participants aged 60 to 84 years, avoiding possible age misclassification. Among these populations, elderly adults with incomplete data for the disability questionnaire screen, serum total bilirubin measurement, household interview or laboratory and clinical examinations were also excluded. Moreover, in order to minimise the confounding effect, we excluded subjects with liver disease or with hepatic function above the normal range, which was defined as serum total bilirubin level ≥22.23 μmol/L (1.300 mg/dL) or serum aspartate aminotransferase (AST) level >40 U/L, serum alanine aminotransferase (ALT) level >40 U/L or serum gamma-glutamyl transferase (GGT) level >55 U/L.

Measurement of serum total bilirubin level

The serum total bilirubin level was determined by automated biochemical profiling (Beckman Synchron LX20 Beckman Coulter Inc., Fullerton, CA, USA); fractionation of total bilirubin was not performed in the NHANES, and bilirubin levels were recorded in milligrams per decilitre. The LX20 uses a timed end-point Diazo method to measure the total bilirubin level. The analytical range for this assay is 0.1 to 30 mg/dL, and the reference range is 0.2 to 1.3 mg/dL.
Functional dependence

All the participants aged 60 years and older were asked 19 questions to evaluate their functional status. These questions were phrased to assess the level of difficulty experienced by the individual in performing physical or mental tasks without using any special equipment. The task covered locomotion and transfers, household productivity, social integration, and manipulation of surroundings and were classified into five major domains: (i) activities of daily living (eating, walking, dressing and getting out of bed), (ii) instrumental activities of daily living (IADL: managing money, housekeeping and food preparation), (iii) leisure and social activities (LSA: attending social events, going out to movies and in-home leisure activities), (iv) lower extremity mobility (LEM: walking one-quarter mile and walking up 10 steps) and (v) general physical activities (GPA: stooping, bending, standing, sitting, lifting, reaching and grasping). For each domain, four levels of difficulties were allowed: no difficulty, some difficulty, much difficulty and unable to perform. Poor performance was defined as having any difficulty in one or more items in a given domain. Functional dependence was defined as having three or more poor performances in the five major domains.

Covariates

Age, sex, race, educational levels and smoking status were obtained by self-report. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres. Diabetes was defined either by a self-report of the physician’s diagnosis, or the presence of a fasting glucose level of ≥126 mg/dL, or the presence of a random glucose level of ≥200 mg/dL, or the use of diabetic medications (including insulin injection or oral hypoglycemic agents). Blood pressure was measured in the right arm unless specific conditions prohibited the use of the right arm. Three and sometimes four blood pressure determinations were taken using a mercury sphygmomanometer by a NHANES physician. Averaged systolic and diastolic blood pressures were obtained. The presence of hypertension was defined either by a self-reported doctor’s diagnosis, or averaged blood pressure of ≥140/90 mmHg, or the use of antihypertensive medications. Comorbidities, including stroke, myocardial infarction, congestive heart failure, angina, chronic bronchitis and arthritis, were ascertained by self-report. Heart disease was defined as if participants had experienced or been told to have myocardial infarction, congestive heart failure or angina. Alcohol intake was determined by the question, ‘In any 1 year, have you had ≥12 drinks of any type of alcohol beverage?’ and was dichotomised.

Ankle-brachial blood pressure index was measured on both sides for participants. PAD was defined as an ankle-brachial blood pressure index of <0.9 on either side. The digit symbol substitution test was the cognitive performance test used in the NHANES. Participants were asked to copy symbols that were paired with numbers in 2 min. The correct numbers of coded symbols, ranging from 0 to 133, were recorded. The 20-ft timed walk test was performed at the participant’s usual pace. Habitual gait speed (m/s) was calculated as walking distance in metres divided by time in seconds. AST, ALT and glucose levels were determined by automated biochemical profiling (Beckman Synchron LX20 Beckman Coulter Inc, Fullerton, CA, USA). The methods used to derive complete blood count parameters, such as white blood cell (WBC) count and haemoglobin, are based on the Beckman Coulter method of counting and sizing, in combination with an automatic diluting and mixing device for sample processing and a single-beam photometer for haemoglobinometry. The total homocysteine level in plasma was measured by the Abbott homocysteine assay (Abbott Park, IL, USA). CRP was analysed using a highly sensitive assay technique and was quantified by utilising latex-enhanced nephelometry with a Behring Nephelometer (Beckman Coulter Inc, Fullerton, CA, IL, USA). Detailed specimen collection and processing instructions are discussed in the NHANES Laboratory Procedures Manual and are available on the NHANES website.

Statistical analyses

The serum total bilirubin levels were normally distributed. Therefore, the individual standard deviation (SD) scores for bilirubin were obtained from the formula \((X_i - Xm)/SD\), where \(X_i\) is the individual value of the bilirubin level in the individual participants, \(Xm\) is the mean value of the total bilirubin level in the study cohort and SD is the standard deviation of the total bilirubin level in the study cohort. We used multiple logistic regression to determine the odds ratios (OR) of functional dependence for a 1-SD increase in the serum total bilirubin level. Moreover, we used quartile-based analysis by dividing serum total bilirubin levels into quartiles with the subjects in the lowest one as the reference group. The cut-off levels for serum total bilirubin quartiles were as follows: Q1 ≤ 0.500 mg/dL, 0.500 mg/dL < Q2 ≤ 0.600 mg/dL, 0.600 mg/dL < Q3 ≤ 0.702 mg/dL and 0.702 mg/dL < Q4 < 1.300 mg/dL. The OR for functional dependence were obtained using multiple logistic regression by comparing each subject in the upper three quartiles of the serum total bilirubin levels to those in the lowest quartile. An extended-model approach was used for covariates adjustment: Model 1 = age, gender, race, educational level;
Model 2 = Model 1 + chronic diseases (hypertension, diabetes, stroke, heart diseases, arthritis, chronic bronchitis, PAD) + health behaviours (alcohol consumption, current smoker); Model 3 = Model 2 + BMI, digit symbol substitution test scores, habitual gait speed; Model 4 = Model 3 + haemoglobin, WBC count, homocysteine, CRP, AST, ALT and GGT levels. Trends tests were assessed by treating the quartiles of serum total bilirubin levels from Q1 to Q4 as a continuous variable in order to observe the associations across increasing quartiles of serum total bilirubin levels and OR of functional dependence. All the analyses were conducted using the Statistics Package for Social Science version 14.0 software (SPSS, Inc., Chicago, IL, USA).

**Results**

**Participants**

The NHANES dataset from 1999 to 2002 had a total of 21,004 participants. Among these subjects, there were 3706 adults aged ≥60 years. We excluded participants aged ≥85 years (n = 409). Furthermore, older adults with incomplete data on the disability questionnaire screen, serum total bilirubin measurement, household interview, or laboratory and clinical examinations were excluded (n = 559). Moreover, in order to minimise the confounding effect, we excluded subjects with liver disease (n = 94) or hepatic function above the normal range, which was defined as serum total bilirubin level ≥1.300 mg/dL (n = 81), serum ALT level >40 U/L (n = 111), serum AST level >40 U/L (n = 54) or serum GGT level >55 U/L (n = 163). Therefore, the final analytic sample consisted of 2235 participants.

**Characteristics of the study population**

The characteristics of the participants as a whole and by quartiles of serum total bilirubin levels are summarised in Table 1. The mean age was 70.54 ± 7.07 and 52.2% of the participants were women. Furthermore, 68.5% of subjects had hypertension and 47.0% had arthritis. Participants with higher serum total bilirubin levels tended to be men, be older in age and have higher BMI, higher haemoglobin level, lower WBC count, lower CRP levels and faster habitual gait speed, as well as lower prevalence of functional dependence in IADL, LSA, LEM and GPA.

**Characteristics pertaining to the status of functional dependence**

There were 230 participants who met the criteria for functional dependence. The characteristics of subjects in the non-functional dependence and functional dependence groups differed for many variables (Table 2). Compared to those with non-functional dependence, participants with functional dependence tended to be older, had poorer cognition, lower haemoglobin level, lower serum total bilirubin level, higher WBC count, higher homocysteine level, higher CRP level, lower gait speed and more chronic diseases, such as diabetes, stroke, heart disease, chronic bronchitis, arthritis and PAD.

**Association between serum total bilirubin level and functional dependence**

The results of the multivariable-adjusted logistic regression between serum total bilirubin levels and functional dependence are provided in Table 3. In the unadjusted analysis, the OR of functional dependence for each SD increment in the serum total bilirubin level was 0.65 (95% confidence interval (CI) = 0.54–0.78, P < 0.001). After adjusting for age, gender, race and education level (Model 1), the OR of functional dependence for each SD increment in the serum total bilirubin level was 0.56 (95% CI = 0.39–0.81, P = 0.002). After additionally adjusting for other covariates in Models 2–4, the inverse association between serum total bilirubin level and functional dependence remained essentially unchanged. The OR of functional dependence for each SD increment in serum total bilirubin level was 0.61 (95% CI = 0.42–0.87, P = 0.008), 0.63 (95% CI = 0.43–0.94, P = 0.023) and 0.62 (95% CI = 0.41–0.94, P = 0.027) from Models 2 to 4 respectively. In other words, a 1-SD increment in the serum total bilirubin level was associated with a 35 to 44% lower likelihood of functional dependence in older adults.

The serum total bilirubin levels were subsequently divided into quartiles and analysed using quartile-based multiple logistic regression (Table 4). Participants with higher quartiles of serum total bilirubin levels tended to have lower odds of functional dependence. The trends of lower likelihood of functional dependence were statistically significant across increasing quartiles of serum total bilirubin levels after additionally adjusting for other covariates from Models 1 to 4 (P < 0.05 for all trends).

**Discussion**

On analysing data from a large, nationwide, non-institutionalised elderly population-based survey, we found that serum total bilirubin levels are inversely associated with the odds of functional dependence after adjusting for basic demographics, chronic diseases, health behaviours and liver function test results, as
### Table 1: Characteristics of study participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartiles of serum total bilirubin levels (mg/dL)</th>
<th>Total n = 2235</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1 = 0.500</td>
<td>Q2 = 0.600</td>
<td>Q3 = 0.702</td>
</tr>
<tr>
<td></td>
<td>n = 584</td>
<td>n = 646</td>
<td>n = 478</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuous variables</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>69.72 (7.00)</td>
<td>70.20 (7.10)</td>
<td>71.08 (7.14)</td>
<td>71.38 (6.96)</td>
<td>70.54 (7.07)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>28.64 (5.71)</td>
<td>28.67 (5.89)</td>
<td>27.99 (5.06)</td>
<td>28.04 (4.94)</td>
<td>28.37 (5.46)</td>
</tr>
<tr>
<td>DSST score, mean (SD)</td>
<td>41.27 (19.15)</td>
<td>43.68 (18.47)</td>
<td>42.95 (19.30)</td>
<td>44.21 (17.43)</td>
<td>43.04 (18.60)</td>
</tr>
<tr>
<td>Hgb (g/dL), mean (SD)</td>
<td>13.46 (1.28)</td>
<td>14.07 (1.35)</td>
<td>14.49 (1.27)</td>
<td>14.70 (1.31)</td>
<td>14.15 (1.39)</td>
</tr>
<tr>
<td>WBC (1000 cells/uL), mean (SD)</td>
<td>7.25 (1.98)</td>
<td>7.07 (2.03)</td>
<td>7.07 (1.89)</td>
<td>6.91 (1.96)</td>
<td>7.08 (1.98)</td>
</tr>
<tr>
<td>Homocysteine (µmol/L), median (IQR)</td>
<td>9.98 (5.26)</td>
<td>10.16 (4.40)</td>
<td>10.26 (3.69)</td>
<td>10.43 (3.69)</td>
<td>10.20 (4.36)</td>
</tr>
<tr>
<td>CRP (mg/dL), median (IQR)</td>
<td>21.00 (7.00)</td>
<td>22.00 (5.00)</td>
<td>22.00 (7.00)</td>
<td>23.00 (7.00)</td>
<td>22.00 (6.00)</td>
</tr>
<tr>
<td>Habitual gait speed (m/s), mean (SD)</td>
<td>2.95 (0.82)</td>
<td>3.07 (0.80)</td>
<td>3.05 (0.96)</td>
<td>3.11 (0.78)</td>
<td>3.05 (0.83)</td>
</tr>
<tr>
<td>AST (U/L), median (IQR)</td>
<td>423 (72.4)</td>
<td>453 (70.1)</td>
<td>306 (64.2)</td>
<td>348 (66.0)</td>
<td>1530 (68.5)</td>
</tr>
<tr>
<td>ALT (U/L), median (IQR)</td>
<td>149 (25.5)</td>
<td>135 (20.9)</td>
<td>80 (16.7)</td>
<td>87 (16.5)</td>
<td>451 (20.2)</td>
</tr>
<tr>
<td>GGT (U/L), median (IQR)</td>
<td>51 (8.8)</td>
<td>37 (5.7)</td>
<td>34 (7.1)</td>
<td>28 (5.3)</td>
<td>150 (6.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical variables</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>190 (32.5)</td>
<td>277 (42.9)</td>
<td>262 (54.8)</td>
<td>340 (64.5)</td>
<td>1069 (47.8)</td>
</tr>
<tr>
<td>Non-Hispanic white, n (%)</td>
<td>278 (47.6)</td>
<td>358 (55.4)</td>
<td>285 (59.6)</td>
<td>337 (63.9)</td>
<td>1258 (56.3)</td>
</tr>
<tr>
<td>Education: high school, n (%)</td>
<td>170 (29.1)</td>
<td>215 (33.3)</td>
<td>176 (36.8)</td>
<td>207 (39.3)</td>
<td>768 (34.4)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>423 (72.4)</td>
<td>453 (70.1)</td>
<td>306 (64.2)</td>
<td>348 (66.0)</td>
<td>1530 (68.5)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>149 (25.5)</td>
<td>135 (20.9)</td>
<td>80 (16.7)</td>
<td>87 (16.5)</td>
<td>451 (20.2)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>51 (8.8)</td>
<td>37 (5.7)</td>
<td>34 (7.1)</td>
<td>28 (5.3)</td>
<td>150 (6.7)</td>
</tr>
<tr>
<td>Heart disease, n (%)</td>
<td>122 (20.9)</td>
<td>111 (17.2)</td>
<td>85 (17.8)</td>
<td>92 (17.5)</td>
<td>410 (18.4)</td>
</tr>
<tr>
<td>Alcohol consumption ≥12 drink/year, n (%)</td>
<td>256 (44.5)</td>
<td>274 (43.2)</td>
<td>201 (42.9)</td>
<td>182 (34.9)</td>
<td>913 (41.9)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>55 (12.6)</td>
<td>55 (12.6)</td>
<td>55 (12.6)</td>
<td>55 (12.6)</td>
<td>288 (14.0)</td>
</tr>
<tr>
<td>Chronic bronchitis, n (%)</td>
<td>45 (7.7)</td>
<td>41 (6.4)</td>
<td>37 (7.8)</td>
<td>30 (5.7)</td>
<td>153 (6.9)</td>
</tr>
<tr>
<td>Arthritis, n (%)</td>
<td>304 (52.1)</td>
<td>298 (46.2)</td>
<td>197 (41.3)</td>
<td>250 (47.5)</td>
<td>1049 (47.0)</td>
</tr>
<tr>
<td>PAD, n (%)</td>
<td>61 (13.2)</td>
<td>64 (11.7)</td>
<td>42 (10.0)</td>
<td>38 (7.8)</td>
<td>205 (11.0)</td>
</tr>
<tr>
<td>Self-reported dependence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADL, n (%)</td>
<td>43 (7.4)</td>
<td>53 (8.2)</td>
<td>16 (3.3)</td>
<td>21 (4.0)</td>
<td>133 (6.0)</td>
</tr>
<tr>
<td>IADL, n (%)</td>
<td>87 (14.9)</td>
<td>81 (12.5)</td>
<td>48 (10.0)</td>
<td>40 (7.6)</td>
<td>256 (11.5)</td>
</tr>
<tr>
<td>LSA, n (%)</td>
<td>72 (12.3)</td>
<td>61 (9.4)</td>
<td>31 (6.5)</td>
<td>27 (5.1)</td>
<td>191 (8.5)</td>
</tr>
<tr>
<td>LEM, n (%)</td>
<td>83 (14.2)</td>
<td>91 (14.1)</td>
<td>47 (9.4)</td>
<td>53 (10.4)</td>
<td>276 (12.3)</td>
</tr>
<tr>
<td>GPA, n (%)</td>
<td>213 (36.5)</td>
<td>213 (36.5)</td>
<td>137 (28.7)</td>
<td>124 (23.5)</td>
<td>647 (30.7)</td>
</tr>
</tbody>
</table>

ADL, activities of daily living; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; DSST, digit symbol substitution test; GGT, gamma-glutamyl transpeptidase; GPA, general physical activities; Hgb, haemoglobin; IADL, instrumental activities of daily living; IQR, interquartile range; LEM, lower extremity mobility; LSA, leisure and social activities; PAD, peripheral artery disease; SD, standard deviation; WBC, white blood cell.
well as for potential inflammatory biomarkers. The anti-inflammatory and antioxidant effects of serum total bilirubin have been regarded as clinically relevant markers of atherosclerotic changes over the past few decades. Many studies revealed inverse associations between the serum total bilirubin level and risk of cardiovascular disease, the prevalence of self-reported stroke and the prevalence of PAD. Le Couteur and colleagues found that a low level of serum ALT may increase the risk of frailty. However, relevant studies exploring the relationships between serum total bilirubin levels and functional dependence are relatively sparse. To the best of our knowledge, this is the first study to provide epidemiological evidence supporting inverse associations between serum total bilirubin levels and functional dependence in an older population.

Bilirubin is an effective antioxidant that successfully scavenges peroxyl radicals and suppresses the oxidation of lipids and lipoproteins, thus acting against plaque formation and subsequent atherosclerosis. Bilirubin also inhibits monocyte transmigration, prevents the formation of oxidised low-density lipoprotein cholesterol, and inhibits endothelial inflammation, vascular smooth muscle proliferation and thrombus formation. Besides being an antioxidant, bilirubin also has cytoprotective properties through its influence on protein kinase C, which increases the scavenger receptor expression in smooth muscle cells and contributes to the formation of

Table 2 Participants characteristics by status of functional dependence

<table>
<thead>
<tr>
<th>Continuous variables</th>
<th>Non-functional dependence n = 2005</th>
<th>Functional dependence n = 230</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>70.20 (6.99)</td>
<td>73.56 (7.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>28.26 (5.27)</td>
<td>29.47 (7.14)</td>
<td>0.005</td>
</tr>
<tr>
<td>DSST score, mean (SD)</td>
<td>43.98 (18.45)</td>
<td>31.18 (16.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hgb (g/dL), mean (SD)</td>
<td>14.19 (1.36)</td>
<td>13.75 (1.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WBC (1000 cells/µL), mean (SD)</td>
<td>7.02 (1.93)</td>
<td>7.52 (2.32)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum total bilirubin (mg/dL), mean (SD)</td>
<td>0.63 (0.20)</td>
<td>0.56 (0.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Homocysteine (µmol/L), median (IQR)</td>
<td>10.02 (4.10)</td>
<td>11.72 (5.97)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/dL), median (IQR)</td>
<td>0.54 (1.12)</td>
<td>0.79 (1.14)</td>
<td>0.002</td>
</tr>
<tr>
<td>Habitual gait speed (m/s), mean (SD)</td>
<td>3.14 (0.78)</td>
<td>2.00 (0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AST (U/L), median (IQR)</td>
<td>22.00 (6.00)</td>
<td>21.00 (6.00)</td>
<td>0.001</td>
</tr>
<tr>
<td>ALT (U/L), median (IQR)</td>
<td>19.00 (8.00)</td>
<td>17.00 (7.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GGT (U/L), median (IQR)</td>
<td>21.00 (13.00)</td>
<td>21.00 (15.00)</td>
<td>0.945</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Categorical variables</th>
<th>Non-functional dependence n (%)</th>
<th>Functional dependence n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>971 (48.4)</td>
<td>98 (42.6)</td>
<td>0.095</td>
</tr>
<tr>
<td>Non-Hispanic white, n (%)</td>
<td>1148 (57.3)</td>
<td>110 (47.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Education &gt; high school, n (%)</td>
<td>721 (36.0)</td>
<td>47 (20.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>1366 (68.2)</td>
<td>164 (71.3)</td>
<td>0.369</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>371 (18.5)</td>
<td>80 (34.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>105 (5.3)</td>
<td>45 (19.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart disease, n (%)</td>
<td>338 (16.9)</td>
<td>72 (31.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol consumption &gt;12 drink/year, n (%)</td>
<td>801 (40.4)</td>
<td>112 (51.6)</td>
<td>0.022</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>248 (13.3)</td>
<td>40 (19.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>Chronic bronchitis, n (%)</td>
<td>118 (5.9)</td>
<td>35 (15.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arthritis, n (%)</td>
<td>900 (45.0)</td>
<td>149 (65.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PAD, n (%)</td>
<td>172 (9.9)</td>
<td>33 (25.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ADL, activities of daily living; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; DSST, digit symbol substitution test; GGT, gamma-glutamyl transpeptidase; GPA, general physical activities; Hgb, haemoglobin; IADL, instrumental activities of daily living; IQR, interquartile range; LEM, lower extremity mobility; LSA, leisure and social activities; PAD, peripheral artery disease; SD, standard deviation; WBC, white blood cell.
Table 3: Association between serum total bilirubin level and functional dependence

<table>
<thead>
<tr>
<th>Model†</th>
<th>OR‡ (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.65 (0.54–0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.56 (0.39–0.81)</td>
<td>0.002</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.61 (0.42–0.87)</td>
<td>0.008</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.63 (0.43–0.94)</td>
<td>0.023</td>
</tr>
<tr>
<td>Model 4</td>
<td>0.62 (0.41–0.94)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

†Adjusted covariates: Model 1 = age, gender, race, educational level. Model 2 = Model 1 + (hypertension, diabetes mellitus, stroke, heart disease) + (alcohol consumption, current smoker) + (arthritis, chronic bronchitis, peripheral artery disease). Model 3 = Model 2 + (body mass index, digit symbol substitution test scores, habitual gait speed). Model 4 = Model 3 + (haemoglobin, white blood cell count, homocysteine, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase). OR‡ indicates odds ratio of functional dependence for 1 standard deviation increment in serum total bilirubin level. OR, odds ratio; CI, confidence interval.

smooth muscle foam cells. Collectively, these findings suggest that bilirubin plays an essential role in tissue protection.

It had been hypothesised that compromised physiological function elicited by chronic inflammation and excessive free radical damage is involved in the pathophysiological process of physical impairments. Both cross-sectional and longitudinal studies have shown associations of high levels of IL-6 and CRP with low physical performance and disability. Ferrucci and colleagues suggested that inflammatory markers may cause a decline in physical functioning through catabolic effects on muscle. In addition, the extent and burden of systemic atherosclerosis resulting in increased cardiovascular risk may give rise to decrease physical performance and to increase functional dependence. Moreover, Masdeu and colleagues suggested that cerebral vascular changes, including a large observable stroke or leukoaraiosis, may develop, and thus interrupt the descending motor fibres arising from medial cortical areas important for lower extremity motor control, as well as debilitate the frontal subcortical circuits responsible for normal gait and balance.

Our findings have several clinical implications. Firstly, in addition to a protective role in specific tissue impairment, our observations shed light on the possible protective effect of the serum total bilirubin level on functional levels. Secondly, to determine independent correlations, serum total bilirubin levels should be taken into account as a confounding covariate for future studies on functional dependence among older adults.

This study also has some potential limitations that deserve acknowledgment. First, because of the cross-sectional study design, causal inference of the serum total bilirubin level to functional dependence could not be established. A further prospective study is necessary to examine the predictability of serum total bilirubin levels for future functional dependence in the elderly. Second, for the purpose of avoiding age misclassification and to minimise the possible confounding effects of hepatobiliary disease, we excluded participants who could contribute to possible selection bias and unsatisfactory generalisation. Third, data regarding potential confounding biomarkers, including direct bilirubin, indirect bilirubin, IL-1, IL-6 and TNF-α, are not available in the NHANES database, and these biomarkers may mediate the association between the serum total bilirubin level and functional dependence in a different way. Finally, we restricted the relevant biomarkers of hepatic function to the normal range; the amplitude of the protective effect on serum total bilirubin levels for functional dependence could therefore not be observed.

Table 4: Association between serum total bilirubin level quartiles and functional dependence

<table>
<thead>
<tr>
<th>Model†</th>
<th>Quartile of serum total bilirubin levels</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1 (OR‡ (95% CI), P-value)</td>
<td>Q2 (OR‡ (95% CI), P-value)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.00 (reference) 0.81 (0.48–1.68) 0.507 (0.46–1.24) 0.751 (0.53–1.30) 0.983 (0.72–1.40) 0.009</td>
<td>1.00 (reference) 0.90 (0.50–1.60) 0.761 (0.53–1.15) 1.154 (0.76–1.75) 0.150</td>
</tr>
</tbody>
</table>

†Adjusted covariates: Model 1 = age, gender, race, educational level. Model 2 = Model 1 + (hypertension, diabetes mellitus, stroke, heart disease) + (alcohol consumption, current smoker) + (arthritis, chronic bronchitis, peripheral artery disease). Model 3 = Model 2 + (body mass index, digit symbol substitution test scores, habitual gait speed). Model 4 = Model 3 + (haemoglobin, white blood cell count, homocysteine, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase). OR‡ indicates odds ratio of functional dependence comparing each subject in the upper three quartiles of serum total bilirubin level to those in the lowest quartile. OR, odds ratio; CI, confidence interval.
Conclusion

In the normal range, the serum total bilirubin level was inversely associated with the odds of functional dependence among community-dwelling older adults in this cross-sectional study. Although a further prospective study is necessary to establish the causality of serum total bilirubin levels to functional dependence, our study provides epidemiologic evidence for future studies on possible interventional strategies for disability prevention in the elderly.

References

Method for identifying eligible individuals for a prevalence survey in the absence of a disease register or population register

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1Health Sciences Centre, University of Canterbury, Departments of 2Medicine and 3Public Health and General Practice, University of Otago, 4Department of Neurology, Christchurch Hospital, Christchurch, New Zealand, 5Department of Geography, University of Exeter, Exeter, UK, and 6Menzies Research Institute, University of Tasmania, Hobart, Tasmania, Australia

Key words
prevalence, data collection, confidentiality, epidemiologic method, population.

Abstract

Background: Identifying eligible individuals for a prevalence survey is difficult in the absence of a disease register or a national population register.

Aim: To develop a method to identify and invite eligible individuals to participate in a national prevalence survey while maintaining confidentiality and complying with privacy legislation.

Methods: A unique identifier (based on date of birth, sex and initials) was developed so that database holders could identify eligible individuals, notify us and invite them on our behalf to participate in a national multiple sclerosis prevalence survey while maintaining confidentiality and complying with privacy legislation.

Results: Several organisations (including central government, health and non-governmental organisations) used the method described to assign unique identifiers to individuals listed on their databases and to forward invitations and consent forms to them. The use of a unique identifier allowed us to recognise and record all the sources of identification for each individual. This prevented double counting or approaching the same individual more than once and facilitated the use of capture–recapture methods to improve the prevalence estimate. Capture–recapture analysis estimated that the method identified over 96% of eligible individuals in this prevalence survey.

Conclusions: This method was developed and used successfully in a national prevalence survey of multiple sclerosis in New Zealand. The method may be useful for prevalence surveys of other diseases in New Zealand and for prevalence surveys in other countries with similar privacy legislation and lack of disease registers and population registers.

Introduction

The number of people with multiple sclerosis (MS) and the extent of disability experienced by people with MS in New Zealand had been unknown until 2010, when the findings of a national prevalence study were reported.1 Earlier studies had provided regional prevalence estimates,2,3 but there had never been a national prevalence study of MS in New Zealand. Accurate prevalence estimates were needed to facilitate the appropriate allocation of resources and planning of services, support and treatment for people with MS in New Zealand.
This paper describes the method we developed to identify and invite eligible individuals to participate in the national prevalence survey of MS in New Zealand. The purpose of the paper is to describe this method in case it might be useful for prevalence surveys of other diseases in New Zealand or for prevalence surveys in other countries with similar privacy legislation and without disease registers or population registers.

Methods

In countries with national population registers, it is possible to identify people with a disease and to estimate the prevalence of that disease using record linkage between the population register and health services databases. A disease register can also provide an estimate of prevalence provided the register is complete and up to date. New Zealand does not have a national population register, and there is no MS disease register. Information about people with MS in New Zealand is held by the Ministry of Health (routinely collected hospital discharge data), in private and public consultant neurologists’ records, and by the Multiple Sclerosis Society (databases at local and national level), but no single organisation holds complete information on all people with MS.

To identify eligible people to participate in the New Zealand MS prevalence survey, we needed information from as many sources as possible to help us identify people with MS. New Zealand privacy legislation meant that the holders of information about people with MS were not permitted to provide us with the names and addresses of people on their databases. Instead, we asked the holders of the databases to assign each individual an identification (ID) number for the prevalence study. The ID number incorporated each person’s date of birth (dd/mm/yyyy), sex (M or F) and the initials of the person’s first given name and surname. Thus, the ID number for a woman with MS named Mary-Jane Katherine Brown who was born on 2 June 1965 is 02061965FMB. We asked the holders of the databases to assign ID numbers in this way and to forward a list of the ID numbers to us. We recorded the ID numbers and asked the holders of the databases to forward a letter from us or make a telephone call to each individual inviting him/her to take part in a confidential survey about MS (the survey was designed to elicit information about demographic characteristics, place of residence at different ages and sunlight exposure). Consultant neurologists who assigned ID numbers also completed a neurological assessment form for each ID number notified, to confirm the diagnosis of MS where possible. If the diagnosis of MS could not be confirmed or the person had not been seen by a neurologist within 12 months, they were directly reviewed by a study neurologist to confirm the diagnosis.

Initially, we had designed the unique identifier to include ethnic group as well as date of birth, sex and initials. Apart from the Ministry of Health hospital discharge database, other databases did not include this information or held incomplete information on ethnic group, so the final version of the unique identifier used in the MS prevalence survey included date of birth, sex and initials only. Questions on ethnic group (using the same questions as the New Zealand census) were included in the questionnaire, so this information was obtained from all participants in the survey. No other changes needed to be made to the design of the unique identifier (Fig. 1).

The use of ID numbers meant that people with MS could be invited to take part in the prevalence study without their identities being revealed to us. It also allowed us to recognise when an individual was included on more than one database. This meant we could avoid approaching the same person twice. When we received an ID number which had already been forwarded to us from another source, the second or subsequent provider of the ID number was asked not to forward a letter to that individual.

We asked the holders of datasets to identify same-sex twins with MS, because this could create duplicate ID numbers if the twins also had the same initials. If this situation occurred, we planned to assign an adjusted ID number (day of birth plus 1 day) for one of each pair of twins and record the existence of the twin pair in our study database. Similarly, in the rare instance of different (non-twin) individuals with identical identifiers, we planned to increase the date of birth by 1 day for one of the individuals and keep a record of this. Neither of these situations occurred in the MS prevalence survey.

In addition to approaching the holders of databases, we advertised the prevalence survey in regional and community newspapers and on local and national radio stations to raise awareness about the survey and to ask people with MS who had not already been approached about the survey to contact us directly using a Freephone number. People with MS who contacted us themselves were assigned an ID number by the study coordinator. The ID number was then used for all study records and data collected, including the questionnaire (see ethical considerations below).

Ethical considerations

Each individual identified from one or more of the sources described earlier was assigned an ID number and then either telephoned or sent a letter by the holder of the database to explain the study, asking if they would be...
Database holders were requested to assign a unique ID number to each individual on their database and forward the ID number to the MS study coordinator.

ID numbers received from:
Multiple Sclerosis Society
Hospital databases
NZ Govt Health Statistics
Neurologists
MS care providers
(Self-reported individuals were assigned ID numbers)

New ID Number
Database holder requested to forward a letter from the MS Study (self-reported individuals were asked to provide contact details so a letter could be forwarded)

Individual invited to take part in MS Study
Informed consent sought

Existing ID Number
Database holder asked not to contact the individual. The identification of that individual by more than one source was recorded for capture-recapture analysis

Diagnosis of MS confirmed
(these individuals were counted in the prevalence estimate)

Questionnaire posted to each individual who had given informed consent

Questionnaire elicited further information (on demographic characteristics and potential risk factors for MS)
prepared to take part in the survey and clinical review if needed. An information sheet and informed consent form were included with each letter (or sent to each person who had agreed to provide their contact details by telephone), and each person contacted was asked to provide his/her name and address and return a signed consent form to the investigators in a prepaid envelope if he/she wished to participate. A separate form asked for permission to contact participants about future research projects and for their views on the establishment of a national register for people with MS.

People who did not wish to participate in the survey were asked to return a confidential form stating that they wished to decline (or for people contacted by telephone, to state that they did not wish to take part). In order to maintain confidentiality, this ‘decline’ form or telephone refusal did not identify the individual, other than by the ID number. If no reply to the initial letter was received within 4 weeks, and a ‘decline’ form had not been received, we asked the relevant database holder to either forward a follow-up letter or telephone the participant on our behalf. If no reply to the second letter was obtained, we asked the database holder to contact the person by phone directly if this was possible and deemed appropriate by the database holder.

Those who gave informed consent to participate in the survey were sent a self-administered questionnaire. They were also asked for permission for their medical records to be assessed by a consultant neurologist (preferably a neurologist they had seen). If an individual had not been seen by a neurologist within 12 months or the diagnosis of definite MS could not be confirmed, they were reviewed by a study neurologist to confirm the diagnosis. The results of the review were recorded and linked to other study data using the unique ID number, so the study neurologists who had made initial notifications from their databases or assessed individuals did not have access to identifying information once the data had been collected, thus maintaining patient confidentiality.

Information linking the names and addresses of study participants with their ID numbers was securely stored in a password-protected computer only accessible to the study investigators and kept in a locked office. Participants were given an assurance that no individual with MS would be identified from any presentations, reports or other publications arising from the research. Approval for the study was obtained from the New Zealand National (Multi-Region) Ethics Committee.

Calculating the prevalence estimate

The point prevalence of MS in New Zealand was estimated by dividing the number of people with clinically definite MS according to the McDonald criteria on ‘the prevalence date’ of 7 March 2006 (the date of the 2006 New Zealand population census) by the number of people usually resident in New Zealand on that date. The resident population was obtained from Statistics New Zealand. It took more than a year to collect information from and assess people with MS in New Zealand, but only those living with clinically definite MS on the prevalence date were included in the prevalence estimate.

Even the most rigorous prevalence surveys fail to identify all people with MS, so capture–recapture methods have been used in other prevalence surveys of MS. Capture–recapture methods utilise multiple data sources to calculate an estimate of the number of people with MS not identified from an individual data source. This allows a more accurate estimate of prevalence to be made, taking into account missing people. The unique ID number developed for the MS prevalence survey allowed us to identify multiple sources of identification for each individual, so we could use capture–recapture methods to improve our estimate of the prevalence of MS in New Zealand.

Results

We found this method worked very well in practice. Five sources (New Zealand government health statistics, District Health Board databases, consultant neurologists’ databases, MS care providers and the Multiple Sclerosis Society databases) used the method described to assign unique identifiers to individuals listed on their databases. ID numbers were also assigned by the study coordinator to individuals who self-notified. The method allowed us to recognise individuals who were listed on more than one database and to include self-referred individuals by assigning unique identifiers to them. The unique identifier allowed us to recognise and record all the sources of identification for each individual, which facilitated the use of capture–recapture methods to improve the prevalence estimate.

The population of New Zealand at the 2006 census was 4 027 950, and we received 13 803 notifications for 5901 individuals (including individuals with definite MS, possible MS, not MS, clinically isolated syndrome and individuals who had died before or were not resident in New Zealand on census day). Of these notifications, 2917 were people with definite MS resident in New Zealand on census day; a prevalence of 72.4 per 100 000 (detailed results, including age and sex-standardised prevalence estimates are provided elsewhere) (Fig. 2). The remaining 2984 of the 5901 individuals notified were not located (547 individuals), had died before census date (1086), were not in New Zealand on the census date (62),...
had been diagnosed after the census date (24) or did not have definite MS (173 had possible MS, 393 had clinically isolated syndromes and 699 did not have MS). We received notification from more than one source for 80.6% of individuals in the study. Capture–recapture analysis estimated that the study had identified 96.7% of people with MS.

A number of individuals in the study had identical dates of birth and sex, but in each instance, the given and surname initials were different, allowing assignment of a unique ID number to each individual. There were no same-sex twins with the same initials. Occasionally, a patient was approached more than once because of an incorrect ID number, and invariably, they let us know of the error, which meant we could correct it. We did not find any potential duplicates or errors of this nature among non-respondents.

Some incorrect dates of birth were detected; these were due to database error or transcription error by the database holder when assigning ID numbers. In most cases, we were able to correct this through cross-checking with another source. For researchers who will be using this ID assignment method in the future, we recommend asking participants to write their date of birth on the questionnaire (we asked for age group only in the questionnaire, because we thought we would already have the date of birth in the ID number), as this would help to verify the correct date of birth for each participant.

**Discussion**

This method allowed us to identify individuals with MS for a national prevalence survey while maintaining confidentiality, complying with privacy legislation and
avoiding double counting. Identification of all the sources of identification for each individual with MS also allowed us to use capture-recapture methods to obtain an accurate estimate of the prevalence of MS in New Zealand.

The advantages of assigning unique ID numbers for the study were:
- It avoided double counting, given that some individuals could be identified from more than one source.
- It prevented us sending multiple letters to people who were listed on more than one database.
- Confidentiality was maintained, so that people who decided not to participate in the survey could not be identified (only those who wished to participate would provide us with their contact details).
- It ensured that those who had already declined to participate did not receive follow-up letters.
- It allowed us to determine whether there were any significant age or sex differences between those who took part in the survey and those who declined (this could be determined because the ID numbers incorporated date of birth and sex).
- It facilitated the use of capture-recapture methods to obtain the most accurate estimate of the national prevalence.

The use of unique ID numbers based on date of birth, sex and initials is appropriate for a prevalence survey, provided the prevalence of the disease or the number of individuals identified is not too high. If the prevalence of a disease or the number of individuals identified is high, it is likely that problems with duplicate ID numbers will occur (because in this situation, several individuals with the disease could be expected to have the same sex, date of birth and initials).

In the case of a small study, concerns that the unique identifier described here would make it possible to identify individuals (through knowing their initials, sex and date of birth) could be addressed by encrypting the unique identifier or assigning a study ID number to each unique identifier. The encrypted or study ID number would have no identifiable components, such as initials or date of birth, and this would provide a further level of confidentiality.

Conclusion

A similar but not identical method of assigning unique ID numbers has been used in New Zealand and other countries to maintain confidentiality in the routine notification of cases of AIDS,11 but to our knowledge, this method has not been used before in prevalence surveys. We believe this method could be useful for researchers wishing to undertake prevalence surveys of other diseases in New Zealand, and for researchers in other countries with similar privacy legislation and lack of disease registers and national population registers.

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We are grateful to the staff of the organisations that helped to identify eligible individuals and to the people who took part in the prevalence survey.

References

Comparison of recommendations for radiotherapy from two contemporaneous thoracic multidisciplinary meeting formats: co-located and video conference

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Key words
lung cancer, multidisciplinary meeting, radiation oncology, video conferencing, rural medicine.

Abstract
Background: Thoracic multidisciplinary meetings (TMDM) are a key component of lung cancer patient management. The optimal design, organisation and function of TMDM are uncertain, and different models may serve different purposes. In the Auckland/Northland region, there are two contemporaneous weekly TMDM using different formats: one is a co-located TMDM (C-TMDM), and the other is a video conference TMDM (V-TMDM) connecting different locations.

Aims: To determine whether the rates of referral for radiotherapy (RT) and concordance between recommendations for RT and actual treatment received differed between the two TMDM formats.

Method: A retrospective review of demographical and clinical data for cases referred for RT from both TMDM between January–June 2009 and the actual RT delivered.

Results: Seventy-nine and 31 lung cancers were referred for RT from the co-located TMDM and the video conference TMDM respectively. While there were significant differences in demographics related to areas of domicile, there were no significant differences between the TMDM in (i) the proportion of cases referred for RT that received RT, (ii) the intent of treatment recommended by the TMDM and the intent of RT delivered, or (iii) transit times to commencement of RT between cases referred from the different TMDM.

Conclusion: The similar results from the different formats of TMDM indicate that cases discussed with the use of e-health technologies are not disadvantaged with respect to recommended therapy nor in the appropriateness of decisions of the TMDM. Use of such technology may reduce the existing disparities in health outcomes between urban and rural patients.

Introduction
Multidisciplinary care (MDC) is an integral component of the management of many chronic conditions. In the management of malignancy, MDC has been shown to improve quality of care. Within the conceptual framework of MDC, the multidisciplinary meeting (MDM) provides the forum for relevant health professionals to implement the key concepts of communication, coordination and decision making. Discussion of cases at the MDM can now be considered a standard of care for the management of lung cancer, which is the leading cause of cancer death in both New Zealand (NZ) and Australia. In lung cancer management, case discussion at the MDM is associated with more consistent decision-making, greater conformity with evidence-based guideline recommendations, a higher proportion of patients receiving active treatment and improved survival.

Although MDM have become a regular feature of lung cancer care, there has been little evaluation of their organisation, structure and function. Difficulties in undertaking research, such as the problems in conducting randomised trials to compare different models, have been identified.

Considerable health disparities exist between urban and rural populations, with poorer health outcomes in rural areas. Factors include shortages and maldistribution of the health workforce, the vast distances of rural Australia and the geographical challenges of NZ, higher out-of-pocket expenses for rural populations, poorer socioeconomic status in rural areas, and reduced access to
a wide range of healthcare. For lung cancer, an excess mortality in those with socioeconomic disadvantage was demonstrated in Australia, and those in rural areas had significantly worse survivals than those in major urban areas (at least for non-Maori) in NZ. Telemedicine, defined as ‘the use of information and communication technology to provide health care services to individuals who are some distance from the health care provider’, is one method to address these disparities. In lung cancer management, telemedicine has the potential to provide MDC in remote areas by providing communication between specialists, independent of geography. Video conferencing facilitates quality care and teamwork across multiple sites while reducing both cost and time requirements. Although telemedicine shares many characteristics of a successful outreach programme for delivering health services, there are only a few disciplines where telemedicine has been shown to be clinically effective. While the Australian telemedicine policy is predicated on such assumptions, there is very little evidence that management delivered using telemedicine provides the same standard level of care as that provided by conventional means.

Radiotherapy (RT) is an important treatment modality in the management of all stages of lung cancer, being used in 40–50% of all cases. A major indication for RT is in the management of patients with locally advanced disease (stage 3) for which guidelines are least prescriptive and where discussions at an MDM might have the greatest influence on management. Thus, treatment decisions about the use of RT may provide a good indicator of clinical decision-making at the MDM.

The availability of two concurrent thoracic MDM (TMDM) with some commonality of participants but of different format within the Auckland region provided the opportunity to compare these TMDM in relation to decisions regarding RT for lung cancer. This study assessed whether concordance with the TMDM decision in a conventional co-located MDM format differed from those in a video conference format and whether there were differences in the access to subsequent treatment.

**Materials and methods**

A retrospective review was performed of cases with primary lung cancer that were presented at either of the TMDM in the Auckland region in the period January–June 2009, with a TMDM recommendation for RT. RT was managed predominantly by a single regional oncology service at Auckland District Health Board (ADHB). This facility served central Auckland, being ADHB, Waitakere District Health Board (WDHB), Counties Manukau District Health Board (CMDHB) and Northland District Health Board. The combined population of these four District Health Boards (DHB) approximates 1.5 million.

During the study period, there were two TMDM held in Auckland, each at weekly intervals. One had a conventional co-located format (C-TMDM), with all TMDM participants in the same room. Most cases presented at the C-TMDM were domiciled in ADHB or WDHB. The other TMDM had a video conference format (V-TMDM), with presentation of cases mainly domiciled in CMDHB. Both TMDM were attended by respiratory physicians, thoracic surgeons, radiation oncologists, medical oncologists and a diagnostic radiologist. All the medical and radiation oncologists (which consist of the same one to two consultants and one advanced trainee for each discipline) attending the V-TMDM also attended the C-TMDM, whereas different groups of respiratory physicians attended each TMDM. For the V-TMDM, respiratory physicians and the diagnostic radiologist were in a studio at CMDHB, and the surgeons and oncologists were in a studio at ADHB. For both TMDM, the relevant clinical history and results of investigations of lung cancer cases were presented, usually by a respiratory physician, followed by a display and description of the relevant images by the diagnostic radiologist. A recommendation was made by consensus regarding the appropriate management. The presenter then referred the patient to the service recommended by the TMDM. The same radiation oncologists attended the TMDM, reviewed cases in clinics and supervised RT delivery.

Cases with primary lung cancer and a TMDM recommendation for RT were obtained from summaries of the weekly TMDM. Demographical characteristics (age, ethnicity, gender and DHB of domicile), tumour factors (histological type and tumour, node, metastasis stage), comorbidity score using the Charlson Comorbidity Index, treatment factors (whether RT was offered, the intent of any RT delivered (curative vs palliative)), and transit times from diagnosis to commencement of RT were obtained from hospital medical records and the RT database. For cases without histological confirmation of malignancy, the date of diagnosis was the date of radiological diagnosis. If presentation at the TMDM within the study period was not for initial management following diagnosis, stage was categorised as ‘recurrence’ and the date of diagnosis was taken as the date of radiological or clinical confirmation of recurrent or progressive disease. Two concordance rates were calculated for cases referred from each TMDM: (i) concordance between the TMDM recommendation and the offer of RT at the radiation oncology clinic, which was the percentage of those referred for RT from the TMDM that were offered RT by the radiation oncologist; and (ii) concordance between TMDM recommendation and actual treatment...
administered that was the percentage of those referred for RT from the TMDM that commenced RT.

Data were double-entered into an Excel database, and discrepancies were checked against the original data sheets and resolved. Data were transferred into an SPSS database for analysis. Statistical analysis was performed using SPSS Version 15 (SPSS, Inc., Chicago, IL, USA). Associations between categorical variables were assessed using Chi-squared (or Fisher’s exact test for small numbers). Univariate and multivariate logistic regression were used to assess factors associated with a dichotomous variable.

Ethical approval for the study was obtained from the Northern X Regional Ethics Committee.

Results
The total number of cases presented at the C-TMDM and V-TMDM was 224 and 107, respectively. Of these cases, 79 and 31, respectively, had a TMDM recommendation for RT. The characteristics of these 110 cases are listed in Table 1.

All cases referred from the V-TMDM had CMDHB as their DHB of domicile, whereas those from the C-TMDM were domiciled predominantly in ADHB and WDHB. As anticipated, there was a statistically significant difference in ethnicity between the TMDM, reflecting the regionalisation of ethnic groups in Auckland, with a significantly higher proportion of the cases referred from CMDHB as compared with ADHB being Māori rather than European \( (P = 0.02) \). All other demographical and tumour factors were similar.

Table 2 shows a comparison of the subsequent course of cases with a recommendation for RT from either TMDM. There were no significant differences between the TMDM with respect to the proportions offered RT, the proportions that received RT or the intent of treatment. The concordance rates for TMDM recommendation and offer of RT at the radiation oncology clinic were 78% and 77% for the C-TMDM and the V-TMDM, respectively, while the concordance rates for TMDM recommendation and receipt of RT were 71% for each TMDM. In 77–84% of cases, RT was delivered with the same intent as recommended by the TMDM. The prescribed treatment course was completed for most cases that commenced RT.

Finally, transit times from diagnosis to commencement of RT were calculated. Although the median transit time from diagnosis to commencement of RT was longer for cases referred from the V-TMDM than from the C-TMDM (64 days (interquartile range (IQR) 23, 86) vs 42 days (IQR 20, 60)), the difference was not statistically significant \( (P = 0.37) \).

Discussion
This study demonstrates that clinical decisions and subsequent treatment do not differ between C-TMDM and V-TMDM. There was no difference between C-TMDM
and V-TMDM in terms of treatment decisions for RT, the concordance rates between the TMDM decision and the offer of RT and subsequent RT. These results add to the scant literature regarding the optimal model for the structure and functioning of MDM and address some of the concerns that have been expressed regarding the impact that technology may have on the functionality of MDM and that it may take a period of time for this technology to be fully integrated.

For logistical reasons, two TMDM have developed independently in the Auckland Region, each with a different format and each serving different referral groups yet referring to the same oncology service. This provided the opportunity to compare clinical indicators between the two forms of presentation while at the same time controlling for differences in oncology staff. The availability of two TMDM of different format conducted weekly and having medical and radiation oncologists in common, provided an opportunity to evaluate the impact of differences in the TMDM format.

There were few differences in demographical or tumour characteristics between patients discussed at the two TMDM. The ethnic differences in the patients reflected those in the community. The largest proportion of patients had locally advanced disease (stage 3). Clinical guidelines are least prescriptive for this group, and thus, it is in this group that one might expect the greatest variation in clinical decision-making. For stage 4 disease, RT has an important role in palliation of symptoms, although clinical judgement is required as to whether an individual patient may be suitable for such treatment. Thus, RT treatment provided a valid indicator to assess TMDM functionality. At the time of the study, most patients with small-cell lung cancer (SCLC) were referred directly to the oncology service without TMDM discussion; subsequently, this situation has changed, and most SCLC are presented at TMDM.

Table 2. Comparison of management of cases with TMDM recommendation for RT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>C-TMDM (79 cases)</th>
<th>V-TMDM (31 cases)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%†</td>
<td>n</td>
</tr>
<tr>
<td>Seen at RO clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>69</td>
<td>87</td>
<td>27</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Offered RT at RO clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>62</td>
<td>78</td>
<td>24</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Patient declined RT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>59</td>
<td>75</td>
<td>24</td>
</tr>
<tr>
<td>Intent of RT when seen at RO clinic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>8</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Palliative</td>
<td>54</td>
<td>68</td>
<td>17</td>
</tr>
<tr>
<td>Unspecified</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Difference in intent of RT between TMDM and RO clinic</td>
<td>13</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Received RT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>56</td>
<td>71</td>
<td>22</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
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<tr>
<td>Completed RT</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>53</td>
<td>67</td>
<td>22</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

†% of the total 79 cases with a C-TMDM recommendation for RT. ‡% of the total 31 cases with a V-TMDM recommendation for RT. *P-value derived from Chi-squared test and Fisher’s exact test was used for categories with small numbers. C-TMDM, co-located format thoracic multidisciplinary meeting; RO, radiation oncology; RT, radiotherapy; TMDM, thoracic multidisciplinary meeting; V-TMDM, video conference format thoracic multidisciplinary meeting.
essentially equivalent concordance rates of 70–80% for TMDM recommendations and RT delivery. The optimal concordance rate has not been determined but will be less than 100% because of factors such as disease progression between MDM and RT assessment, full assessment of morbidities in relation to the recommended treatment, and a more detailed assessment of patient preferences. From the combined cohort of the TMDM in this study, the main contributor to discordance was disease progression, with 6% of cases deteriorated or died prior to the consultation. Following consultation, 10% of cases were not offered RT. Reasons include patients being asymptomatic or had minimal or controlled symptoms, had already commenced chemotherapy or had disease or symptoms that were too extensive for RT.

Second, the value of the V-TMDM would be compromised if it was associated with increased delay for recommended therapy. Although not statistically significant, the median time from diagnosis to commencement of RT was longer for cases presented at V-TMDM. Further studies are required to confirm that treatment decisions made through telemedicine technology provide equal subsequent access to healthcare services. Only if this is the case might some of the health disparities between rural and urban patients be addressed.

This study addressed the use of telemedicine for clinical decision-making within an MDM. However, the scope of telemedicine to impact healthcare for rural patients either directly or indirectly is much greater. Telemedicine may provide (i) patients with improved access to specialist healthcare, improved quality and access to services; (ii) rural health professionals with local access to continuing education and professional development, enhanced local service provision, more rapid specialist input, increased support from and access to specialists, enhanced experiential learning, networking and collaborations; (iii) hospitals with reduced travel and other costs; and (iv) society with improved health and well-being of those in rural areas. All these aspects are relevant to the management of lung cancer.

This study had the usual limitations of a retrospective review. While a number of factors may have influenced clinical decision-making and only some of these were ‘controlled’, the remarkable concordance of all the clinical indicators suggests equivalence of the TMDM. The study was also limited by restriction to RT decisions. Verification of these findings for the other treatment modalities in the thoracic oncology service should be undertaken.

**Conclusion**

This is the first comparison of TMDM of different formats in which an assessment of the impact of the format was possible, as many other potentially important variables were controlled. The results have shown equivalent outcomes in terms of the proportions offered RT, the proportions that received RT or the intent of treatment, the concordance of a recommendation for RT, and subsequent delivery of RT and transit times to treatment did not differ significantly. These findings indicate that patients were not disadvantaged by the V-TMDM format and received an equivalent MDM RT treatment plan formation as those discussed at the co-located format. These findings have relevance for the future design of MDM, particularly in NZ and Australia, where small, widely dispersed populations and health facilities make teleconferencing an attractive option and provide support for the expanded use of telemedicine to deliver quality services to remote and rural communities.

**References**


11 Dixon J, Welch N. Researching the rural-metropolitan health differential

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Abstract

Background: The background of the study is a comparison of risk-adjusted mortality across hospitals from different jurisdictions is now common worldwide.

Aim: To examine temporal trends in risk-adjusted mortality in Victoria over the last decade.

Methods: Retrospective cohort study of 6.89 million adult (>14 years) patient episodes from 23 major Victorian public hospitals between 1999 and 2009. The primary outcome was in-hospital death. Three measures were calculated: the crude mortality rate, risk-adjusted mortality rate and standardised mortality ratio (SMR). The Hospital Outcome Prediction Equation (HOPE) was applied to generate estimates of predicted mortality that were used to compute the SMR and risk-adjusted mortality rates. The HOPE model includes 26 exogenous risk factors for which providers have no influence. The model was calibrated using the 2004–2005 data. Temporal mortality trends from 1999–2009 were evaluated using negative binomial regression for crude mortality and SMR estimates and random-intercept hierarchical logistic regression for risk-adjusted mortality.

Results: The study population included 84,423 in-hospital deaths (1.2%). Crude mortality risk declined from 1.5% in 2000 to 1.1% in 2005–2009 (incidence rate ratio (IRR): 0.96; 95% confidence interval (CI): 0.95–0.97; P < 0.001). There were 1.39 million episodes in the HOPE calibration cohort. Between 1999 and 2009, the SMR decreased from 1.4 to 0.9 (IRR = 0.91; 95% CI: 0.90–0.97; P < 0.001) and adjusted mortality risk declined from 2.1% to 0.9% (odds ratio = 0.94, 95% CI: 0.94–0.94, P < 0.001). Declining mortality trends were evident in the tertiary, metropolitan and regional peer groups (P < 0.001).

Conclusion: Analysis of in-hospital risk-adjusted mortality trends using the HOPE model indicates significant improvement in patient outcomes in the State of Victoria over the past decade.
Introduction

Review of a hospital’s clinical performance is an integral part of healthcare delivery and reform. Most commonly, overall performance is measured with a focus on safety. Mortality is an outcome of importance to patients, clinicians, service providers and funding bodies. It is easily defined and routinely collected in hospital administrative data. Comparison of mortality outcomes that adjust for patient characteristics (risk-adjusted mortality) across hospitals from different jurisdictions is common. Risk-adjusted mortality statistics are presently reported in the UK, Sweden, The Netherlands, Canada and the USA. In November 2009, the Australian Health Ministers endorsed risk-adjusted mortality as a key indicator of hospital-level performance in Australia.

While it is not possible to prevent all in-hospital deaths, nor is it unexpected for some patients, it is reasonable for healthcare administrators and the community to seek reassurances that hospital mortality rates fall within an acceptable benchmark. This study aimed to address this need by providing insights into risk-adjusted mortality trends in Victorian public hospitals over the last decade.

We have previously demonstrated that the Hospital Outcome Prediction Equation (HOPE) may be a reliable predictor of in-hospital mortality in major hospitals within the State of Victoria. The HOPE model can be applied to routinely collected patient data incorporated in administrative datasets. The HOPE model includes 26 exogenous risk factors for which healthcare providers have no influence. The objective of this study was to evaluate the temporal trends in risk-adjusted in-hospital mortality in major Victorian public hospitals between 1999 and 2009.

Methods

The Victorian Department of Health provided the dataset and approved this publication.

Design, setting and sample

A retrospective cohort study of 6.89 million adult (>14 years) episodes from 23 Victorian public hospitals between 1 July 1999 and 30 June 2009 was undertaken.

Source data

Demographic and clinical data extracted from the Victorian Admitted Episode Database (VAED), an administrative dataset extracted by qualified data-collections from clinical records, chiefly for the purpose of determining hospital funding. Since 1998, clinical information in the VAED has been coded using the International Classification of Diseases, 10th Revision, Australian Modification (ICD-10-AM). Good to excellent coding quality of ICD-10-AM has been demonstrated for principal procedure codes, many diagnostic codes, and coding of comorbid diagnoses.

Acute-care separations, including obstetric and same-day procedures, from all major public hospitals in the State of Victoria were included in the analysis. A major hospital was defined as an acute-care hospital with 24-h onsite emergency and intensive care services. Paediatric hospitals and patients (<15 years), sub-acute and palliative care admissions were excluded.

Main outcome measures

The primary outcome was in-hospital mortality. The HOPE model was applied to generate estimates of predicted mortality that were used to compute risk-adjusted mortality rates and standardised mortality ratios (SMRs). The HOPE model includes four demographic variables (age, emergency admission and transfer from other hospital or an aged-care facility) and 22 primary admission diagnosis categories. The HOPE model was calibrated using the central 12-month cohort (2004–2005).

The patient episode characteristics included in the HOPE model were generated from VAED fields. Age was coded in 5-year age subgroups. Primary admission diagnoses are coded using ICD-10-AM coded diagnoses and are accompanied by a ‘P’ condition onset code. Admission variables (emergency, transfer from other hospital or an aged-care facility) and mortality were generated from the VAED ‘admission type’, ‘admission source’ and ‘discharge mode’ fields.

Statistical analysis

Three measures of in-hospital mortality were calculated. These were (i) the crude mortality rate (observed deaths as a percentage of total episodes for the selected cohort), (ii) risk-adjusted mortality rate and (iii) the SMR. Descriptive statistics were used to profile sample demographics and in-hospital mortality aggregated by each year of observation. The HOPE model was applied to the data to generate the predicted probability of in-hospital death for each patient episode. These predicted probabilities were then used to generate the SMR and risk-adjusted mortality rates. Dividing the observed deaths by the predicted deaths generated the SMR value, and multiplying the crude mortality rate by the SMR generated

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the risk-adjusted mortality rate for each cohort. A SMR value of 1.0 is equivalent to the benchmark, and a SMR above (or below) 1.0 indicates the mortality rate is above (or below) the benchmark.

Crude mortality rates, SMR and risk-adjusted mortality rates along with 95% confidence intervals (CI) were generated for the entire sample and hospital peer groups for each consecutive year.

Temporal trends in crude mortality rates and the SMR were assessed using negative binomial regression models. For each mortality parameter (crude mortality or SMR), four models were generated – one for each of the three peer groups and another, including all 23 hospitals. Deaths and SMR values were aggregated by the unit of analysis (peer group or total sample). Robust standard errors were used to provide some degree of adjustment for patient level clusters in the data.

In the crude mortality analysis, the hospital mortality was the dependent variable, the year of observation the explanatory variable and the number of admissions the exposure variable. In the SMR model, the SMR value was the dependent variable, the year of observation the explanatory variable and the number of admissions the exposure variable.

Temporal trends in risk-adjusted mortality were assessed with a random-intercept hierarchical logistic regression model based on patient level data. These models adjust for hospital level clusters. Once again, four models were generated for each of the peer groups and another, including all 23 hospitals. Hospital mortality was the dependent variable, and the year of observation and HOPE predicted mortality the explanatory variables.

These models are increasingly used to analyse multi-level outcome data, such as patient data that are aggregated by hospitals. They are appropriate for patient level data and enable inferences at the hospital level by adjusting for the ‘clustering’ of patients with similar characteristics. Clustering can occur at several levels. For example, a patient may be admitted multiple times during the observation period, especially chronic disease and elderly patients. Multiple admission episodes create data clusters – observations that are not independent. Clustering can also occur at the unit level where patients have similar characteristics, for example neurological diagnosis, creating dependence between observations. Failure to adjust for clustering can result in incorrect associations being identified.

Temporal linearity assumptions were tested using the year variable. Associations were reported as incidence rate ratios (IRR) for the negative binomial regression results and odds ratios (OR) for the logistic regression results. A P-value of ≤0.05 was considered to be statistically significant and CIs were calculated at the 95% level.

The negative binomial models used robust estimates for the standard errors to account for some level of clustering of episodes within patients. Results are presented for the entire sample and aggregated by peer group. Peer groups included tertiary referral (‘tertiary’; \( n = 6 \)), non-tertiary metropolitan (‘metropolitan’; \( n = 7 \)) and regional hospitals (‘regional’; \( n = 10 \)).

Graphical presentations of temporal trends included the crude mortality rate, average risk of death (predicted deaths) and the risk-adjusted mortality rate.

Data analysis was undertaken using Stata/MP v11 software (StataCorp, College Station, TX, USA).

**Results**

**Study population**

The State of Victoria has 141 public hospitals serving a population of approximately 5.31 million. Between 1 July 1999 and 30 June 2009, there were 12.40 million hospital separations (prevalence 24.4 per 10^5 population) reported from the 141 public hospitals. Twenty-three (16%) of these hospitals, with on-site emergency and (adult) intensive care services, reported 7.68 million separations (62%; Table 1). One of these hospitals commenced data submission in the second year of the study.

After exclusion of paediatric, sub-acute care and those without a primary diagnosis (103 episodes; 0.001%), there were 6.89 million patient episodes included in the analysis. Of these, 48% were from tertiary, 31% from metropolitan and 21% from regional hospitals. There were no other missing data. There was a significant increase in risk of death (predicted death) \((P < 0.001)\) and decline in length of stay \((P < 0.001)\) over the 10-year period (Table 1), without a change in the proportion (58%) of same-day cases \((P = 0.16\) for trend).

**Mortality trends**

The study population included 84,423 in-hospital deaths (1.2%). Crude mortality risk declined from 1.5% in 1999–2000 to 1.1% in 2008–2009 (IRR: 0.96; 95% CI: 0.95–0.97; \( P < 0.001 \)) (Fig. 1). There were 1.39 million episodes in the HOPE calibration cohort (Table 2). Between 1999 and 2009 the SMR decreased from 1.4 to 0.9 (IRR = 0.91; 95% CI: 0.90–0.92; \( P < 0.001 \)). For the same period risk-adjusted mortality declined from 2.1% to 0.9% (OR = 0.94, 95% CI: 0.94–0.94, \( P < 0.001 \)). Declining mortality trends were evident in all three peer groups \((P < 0.001); Table 2\).

Table 3 lists the top 10 diagnostic categories for mortality and together they include 15.1% of separations and 61.0% of all fatalities. Eight of these diagnostic subgroups...
demonstrated a significant decline in mortality rate. The two exceptions were the mortality rates for metastatic malignancies and sepsis-related conditions.

Discussion

Measuring and comparing hospital outcomes is one of several potential clinical indicators of performance in hospitals and healthcare systems.\(^5\),\(^10\) It provides a tool that may provide insight into the process and quality of care. We undertook an analysis of risk-adjusted mortality in all 23 adult acute public hospitals with the State of Victoria over a 10-year period. We found a significant decrease in both hospital crude and adjusted mortality rates (Table 1, Fig. 1) despite an increase in patient complexity (predicted risk). These observations were mirrored in the three peer groups, in 18 (78\%) hospitals and in eight of the top 10 mortality diagnoses.

Analysis of statewide risk-adjusted mortality affords us several useful insights. The sustained reduction in both hospital length of stay (LOS) and mortality suggest there is likely to have been an improvement in the quality of acute healthcare in Victoria. Several other plausible explanations are worthy of discussion. These include an increase in low acuity admissions, an increase in hospital readmission rates, coding and casemix drift, and transfer of dying patients to sub-acute and palliative care institutions.

An increase in low-acuity or day-case admissions is not supported by our data. If either was present, we expected to see a fall in the predicted risk of death whereas the results indicate the opposite. Although the number of day-case admissions increased substantially over time, the proportion (of day-cases to total episodes) remained static.

Coding and casemix drift can be excluded on the basis of this analysis of the VAED, demonstrating consistency in casemix\(^9\) and model coefficients over the 10 years. Even if a drift in casemix, or low-acuity admission or readmission rates had occurred we would expect this to be adjusted following annual recalibration of our risk-adjustment model.

The early transfer of elderly or dying patients to sub-acute and palliative care services is another possible explanation. We believe this is an unlikely explanation because mortality rates in the excluded health services and the overall state mortality also fell (results not shown).
We are therefore left with the plausible conclusion that improvements in the quality of care have led to a fall in both LOS and mortality. Numerous healthcare initiatives during the study period may explain our findings. These include the introduction of a State Trauma System, improved access to percutaneous coronary invention and introduction of rapid-response and medical emergency teams; expansion of minimally invasive surgical techniques, together with clinical review and quality audit programmes. Our results are likely to reflect the high standard of care provided by the Victorian public hospital system and may provide some reassurance to the community and healthcare administrators of the cost-benefit of acute health services.

We should, however, caution against assuming that the healthcare system is trouble free. Nor should we assume that patient care will inevitably continue to improve and will not decline in the future. This is one reason why constant monitoring of clinical outcomes and patient safety is necessary.

The HOPE model has several attractive features: it is based on dichotomous variables (except for age) that are both present at the time of admission and independent of clinical intervention or therapy. It is derived from data collected by health jurisdictions in all States of Australia. The data is collected (in Victoria) by qualified and trained Health Information Managers who are independent of the treating clinicians.

The HOPE model has several limitations. It is yet to be validated in other States and in smaller-sized

Table 2 Annual decline in mortality, 2000–2009

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<tr>
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<th>Crude mortality†</th>
<th>Standardised mortality ratio†</th>
<th>Risk-adjusted mortality‡</th>
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<td>Year incidence rate ratio (95% confidence interval)</td>
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<td>Crude mortality†</td>
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<td>All</td>
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<td>Tertiary</td>
<td>0.96 (0.95–0.97)</td>
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<td>Regional</td>
<td>0.96 (0.95–0.97)</td>
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<td>Metropolitan</td>
<td>0.95 (0.94–0.96)</td>
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<tr>
<td>Standardised mortality ratio†</td>
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<td>All</td>
<td>0.91 (0.90–0.92)</td>
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<td>Metropolitan</td>
<td>0.94 (0.93–0.94)</td>
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†Results obtained from negative binomial regression based on data aggregated at the peer group and total sample levels. †Results obtained from patient episode level hierarchical logistic regression based on patient level data.

Table 3 Top 10 state mortality diagnoses and *analysis of trend for a decrease in annual risk-adjusted mortality over 10 years

<table>
<thead>
<tr>
<th>Diagnosis (ICD-10-AM prefix)</th>
<th>Mortality (%)</th>
<th>P-value*</th>
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<tbody>
<tr>
<td>Septicaemia (A40–A41)</td>
<td>15.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Cerebrovascular diseases (I6)</td>
<td>14.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Respiratory disease-Other (J6–J9)</td>
<td>10.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Pneumonia (J13–J18)</td>
<td>8.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart diseases, other (I50–I52)</td>
<td>6.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute myocardial infarction (I21)</td>
<td>6.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Secondary malignancy (C76–79)</td>
<td>5.67</td>
<td>0.13</td>
</tr>
<tr>
<td>Gastric and intestinal diseases (K25–K27, K55–K56, K63–K67, K9)</td>
<td>3.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Chronic lower respiratory disease (I4)</td>
<td>3.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Trauma and injury (S1–S9)</td>
<td>1.1</td>
<td>0.001</td>
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ICD-10-AM, International Classification of Diseases, 10th Revision, Australian Modification.
hospitals, where monitoring of patient care and outcomes is equally, if not more, important. The model excludes paediatric and sub-acute care where more common outcome measures (other than mortality) must be sought. Further work is required to develop statewide clinical indicators appropriate to these groups.

If the hospital SMR were to be reported as a national clinical indicator, our analysis reveals some important insights and caveats. First, analysis of the data is complex and relies on accurate and comprehensive data and sound risk-adjustment methods. The HOPE model may be one such tool. Second, a single SMR value, or group of static SMR values, is likely to be misleading and subject to over-reporting of outliers. Much more valuable is the information provided by a continuous analysis using more than one benchmark over several years. A true outlier whose performance is improving is more reassuring than an apparent inlier that is deteriorating.

Conclusion

We have demonstrated that longitudinal analysis of risk-adjusted mortality provides useful information about acute healthcare performance and demonstrates improved quality of care in the Victorian public healthcare system over the previous 10 years. The HOPE model appears to be a useful risk-adjustment method in a large and diverse hospital population within the State of Victoria. It may be applicable in other States of Australia, but further analysis is required before it is more widely adopted. Further work is required to refine outcome prediction models and investigate long-term outcome measures other than mortality.

Acknowledgements

With thanks to Qianlin Zhang (Northern Clinical Research Centre, Melbourne) for assistance in preparation of the manuscript, to the Department of Health (Victoria) for providing access to the VAED, to the Health Information Managers who extract the coding data from medical records, and to the clinical staff of the public healthcare system for their hard work and dedication in the delivery of high-quality care.

References

Access to anticancer drugs: many evidence-based treatments are off-label and unfunded by the Pharmaceutical Benefits Scheme

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Key words
oncology, haematology, off-label, unlicensed, chemotherapy, PBS.

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Abstract

Background: The off-label use of a drug refers to a use outside the terms of its approval by the Therapeutic Goods Administration (TGA). It is also possible to prescribe unlicensed drugs under the TGA’s special access scheme. A high rate of off-label prescribing has previously been reported in cancer. Our study aimed to document the disparity between evidence-based clinical guidelines for anticancer therapy, product approval and funding status of these agents within an academic tertiary/quaternary cancer centre.

Methods: All chemotherapy protocols approved for use in our specialist oncology centre were assessed to determine if the drugs were off-label or unlicensed for that indication based on review of their current product information. The Pharmaceutical Benefits Scheme (PBS) funding status for each protocol was subsequently assessed.

Results: A total of 448 protocols containing 82 different drugs across 15 tumour groups was identified. Overall, 189 (42.2%) of protocols were off-label, and three (0.7%) were unlicensed. This resulted in all 192 protocols being unfunded by the PBS. Of the 189 off-label protocols, 132 (69.9%) were based on established evidence-based treatment guidelines, and a further 39 (20.6%) was based on phase II or III clinical trial data.

Conclusion: Over 90% of off-label protocols are supported by established treatment guidelines or published peer-reviewed research even though the medications are not approved for that particular use by the TGA. However, these off-label protocols are unfunded by the PBS; this results in a marked inequality of access to appropriate medications for cancer patients across Australia.

Introduction

There is a high prevalence of off-label prescribing in the cancer setting, where substantial differences exist between indications approved by regulatory authorities and the standards in clinical practice.1–3 Off-label prescribing refers to the use of a drug, which has been approved by the Therapeutic Goods Administration (TGA), for indications that fall outside the terms of the official ‘labelling’ or product approval. The TGA assesses the safety and efficacy of drugs for each specific use, a process entirely separate to an application for government reimbursement of a drug. A prescription may be off-label for a number of different reasons, including indication, dose, combination of medications, schedule and route of administration, as well as duration and line of treatment.4 Many physicians prescribe in this manner, generally based on a high level of evidence, when there are no suitable alternatives, and it may be the only treatment option for cancer patients.5

The use of unlicensed anticancer drugs (drugs that have not been approved for any indication) is less common. In Australia, this is made possible under the TGA’s special access scheme. A drug may be unlicensed because it has never been submitted for evaluation, it has been evaluated and rejected by the TGA, or the sponsor has withdrawn the drug from the market (forced or voluntarily). The lack of regulatory approval for a specific indication does not imply that the TGA disapproves of an off-label use but rather indicates that they have not reviewed the use of that particular medication in the clinical setting concerned. This often arises as the sponsoring pharmaceutical company has not submitted the agent for that specific indication (for logistical or market issues) or the agent is off-patent. The companies have no
It is important to note that off-label and/or unlicensed prescribing is not necessarily unsupported by clinical data, of variable quality and often does form part of standard treatment guidelines. Furthermore, these drugs may have been approved in another jurisdiction, for example the Food and Drug Administration (FDA) in the USA.

Patients need access to beneficial off-label treatments that are based on scientific evidence, but at the same time, they require protection from off-label interventions that are risky and ineffective. While it is preferable that all uses of drugs and devices are supported by research, this is not always available or feasible. Thus, it is the responsibility of the prescriber to ensure that any off-label use of a drug or device is truly appropriate.

An Australian study, which examined the prevalence of off-label or unlicensed prescribing at a specialist cancer hospital, found that between 2001 and 2008, prevalence increased from 22% to 39% (expressed as a percentage of total prescriptions), and in 2008, 85% of patients were prescribed at least one drug that was unlicensed or off-label. This study included all drugs: anticancer drugs, supportive care drugs and drugs not directly related to cancer. An American study that analysed the records of 185,000 cancer patients between 2003 and 2008 reported that 68% of breast cancer patients and 95% of lung and bladder cancer patients were prescribed drugs, which were not FDA-approved for these cancers. However, the majority of patients (99.7%) received treatment within the National Comprehensive Cancer Network (NCCN) guidelines, illustrating the level of disparity between standard treatment guidelines and regulatory-approved indications. These prescribing patterns were also supported by an Italian study.

In addition to the therapeutic issues associated with the off-label drugs, there are also cost factors that need to be discussed with patients. The Pharmaceutical Benefits Scheme (PBS) lists certain drugs recommended by the Pharmaceutical Benefits Advisory Committee for reimbursement based on cost-effectiveness. The listing of a drug may be unrestricted (but limited to TGA-approved indications) or may be restricted to certain indications, which may be narrower than the TGA approval. It is important to note that a drug cannot be listed or reimbursed under the PBS for an unapproved (off-label) indication, that is, they require licensing for that indication by the TGA.

Our study aimed to determine the proportion of chemotherapy protocols used in a specialist cancer hospital that include off-label and unlicensed prescribing. Furthermore, we aimed to identify which of these drugs are a part of established treatment guidelines even though they are not approved by the TGA and therefore unfunded by the PBS.

### Methods

A complete list of chemotherapy protocols used at the Peter MacCallum Cancer Centre was obtained from CHARM (Charmhealth, Bardon, Qld, Australia), a cancer medicines management software programme. Protocols were added to the programme from November 2008 onwards. Protocols were incorporated by the relevant haematology and medical oncology subspecialty group based on the highest level of evidence for each indication derived from national and international guidelines, meta-analyses, phase III trials, etc., and are reviewed on an annual basis.

Each protocol was analysed, and the drugs forming each protocol were compared against their approved indications (and approved combination of drugs, where applicable) according to the current Australian product information for all brands of the drug (sourced from MIMS and the TGA website) in addition to the PBS criteria for their reimbursement status (from the PBS website). This comparison was performed during December 2010. Clinical trial protocols and protocols for supportive therapy (e.g. iron infusions for the treatment of anaemia) were excluded. All other protocols were included in the analysis.

Within each protocol, drugs were categorised as being licensed (approved by TGA for that specific indication), off-label (TGA-approved for other indications or disease settings) or unlicensed (not TGA-approved). The drugs were also categorised according to their PBS reimbursement status as either funded (divided into restricted or unrestricted) or unfunded. Indication (i.e. cancer type) and drug combinations were considered when categorising drugs and protocols. When categorising drugs, the disease setting for which they were approved (or PBS funded) was taken into account, that is, if only for adjuvant therapy or only for metastatic disease. Factors such as dose, infusion rates, dosage form and place in therapy (e.g. as first-line therapy or as treatment for refractory disease in the metastatic setting, etc.) were not considered.

For each protocol, if one or more drugs were off-label, then the protocol was considered off-label (or unlicensed where applicable). The same principle was applied to PBS listing: if one or more drugs in a particular protocol were not eligible for PBS funding, then the protocol was considered to be unfunded.

Where a protocol was considered off-label or unlicensed, a search of established cancer treatment...
guidelines was conducted to verify the level of clinical evidence for that particular regimen. Guidelines consulted included those of the NCCN, British Columbia Cancer Agency, Cancer Care Ontario and the New South Wales Cancer Institute (eviQ database). Where protocols were not contained within any established consensus guidelines, a primary literature search was conducted to determine the highest level of available evidence for its use. Primary literature searching was conducted using the Medline and EMBASE databases.

**Results**

A total of 448 protocols, containing combinations of 82 different drugs, was included in the analysis. One hundred and ninety-two protocols (42.9%) contained at least one drug that was being used in an off-label or unlicensed indication or was being used in an off-label combination. Therefore, all 192 protocols are unfunded by the PBS. Of those 189, off-label protocols (i) 132 (69.9%) were supported by evidence from one or more established cancer treatment guidelines, (ii) 39 off-label protocols (20.6%) were based on phase II or III clinical trials, and (iii) 18 (9.5%) protocols had no available published evidence to support their use for the indication in which they were being used (Fig. 1).

Over 50% of off-label protocols were identified for the following malignancies: head and neck, central nervous system, skin, gastrointestinal, gynaecological, lung, transplantation/mobilisation, and sarcoma. The majority of these having protocols were based on established treatment guidelines ranging 60–90%.

Three protocols (0.7%) contained drugs that are unlicensed in Australia. The three protocols containing unlicensed drugs were not found in any established guidelines but were supported by primary research reports (Table 1).

In the 6 months from 1 July 2010 to 31 December 2010, 234 of the 448 protocols had been prescribed for at least one cycle of treatment. The remaining 214 protocols remained as options within CHARM but had not been used within the selected 6-month period.

**Discussion**

Off-label prescribing is an integral part of patient care in cancer. The results of this study demonstrate that while the incidence of off-label prescribing is high, the majority of off-label chemotherapy prescribing is supported by established clinical guidelines or evidence from primary research reports. A much smaller number of protocols was supported by lower levels of evidence, such as phase II trials. A significantly smaller number of protocols had no published evidence available to support their use for their intended indication; however, most of these protocols (drug combinations, doses, etc.) were available in guidelines or published primary literature for other diseases. This suggests that in certain instances, off-label prescribing may be based on extrapolation of clinical data supporting the efficacy of a therapy in one cancer to other cancers with similar pathophysiology, for example, head and neck squamous cell carcinoma (SCC) therapies are used in the treatment of SCC of the skin.

Off-label prescribing of drugs has been reported for most types of cancer but may be more common in certain types of malignancy. For example, other studies have reported a lower incidence of off-label prescribing in breast cancer when compared with bladder cancer or hormone-refractory prostate cancer. Furthermore, off-label use of drugs was higher in cases where there was no consensus on the optimum therapy, and patients with metastatic and advanced forms of rare malignancies. Off-label use is also more likely to be seen for drugs with a narrow range of indications but with a broad spectrum of activity.

Due to the aggressive nature of some cancers, prescribers may be more likely to consider off-label drug use, especially for patients where all other licensed treatment options may have been exhausted. Our analysis found that tumour types, such as breast and leukaemia, had a lower incidence of off-label drug use than some of the
rarer tumours perhaps reflecting the greater availability of licensed drugs in these settings.

Lack of regulatory approval for chemotherapy drugs may be, in part, due to difficulty in obtaining the required level of evidence to support an application for approval. For rare cancers, it may be difficult to obtain sufficient numbers of participants to generate high-quality clinical trial data for an approval submission. For treatments for such tumours, the TGA approval may seem an unrealistic goal, unless it was obtained through the orphan drugs pathway. Orphan drugs are defined by the TGA as a drug that is intended to treat, prevent or diagnose a rare disease or condition. On the other hand, even where high-level clinical data exist for a rare cancer, pharmaceutical companies may be reluctant to submit for licensing for marketing reasons or where the drug has come off-patent. Pharmaceutical companies are not mandated to submit to any regulatory process, but on the other hand, they are the only organisations that have the resources to enable a submission.

This study demonstrated that a large proportion of protocols that were not TGA-approved was included in evidence-based clinical guidelines (in many cases, from multiple institutions). This indicates that there is a substantial, thus unacceptable, delay between incorporation of clinical evidence into standard practice and/or guidelines and regulatory approval. Cancer is a very research-intensive area of medicine, and as such, the best available evidence is rapidly changing, along with trends in standard treatments. Lengthy government approval processes that drugs must be subjected to may be inappropriate in a cancer setting and result in failure to incorporate the most recently available evidence in a timely fashion. This may be problematic for prescribers who utilise the official product information to guide their prescribing decisions, as TGA-approved product information often does not contain the most current or best available evidence.

Following initial TGA approval of a drug, the TGA will only incorporate additional indications if the company resubmits the drug for approval for use in these additional indications. This process is costly and time-consuming for pharmaceutical companies, and is often not undertaken. This is particularly so if there is perceived to be little financial incentive, but as well the companies are under no legal obligation to submit new indications or change the product information. This may be the case for older drugs that are not TGA-approved for certain indications, or older drugs that are not TGA-approved for certain indications, or older drugs that are not TGA-approved on the market at all. This is particularly relevant where generic versions are available. This has resulted, in older versions of the same drug, in a lack of regulatory approval in some settings. Lack of regulatory approval for chemotherapy drugs may be, in part, due to difficulty in obtaining the required level of evidence to support an application for approval.

### Table 1
Summary of off-label protocols (by tumour stream) and the level of evidence to support their use

<table>
<thead>
<tr>
<th>Tumour group</th>
<th>Total no. protocols</th>
<th>No. off-label protocols (%)</th>
<th>No. off-label protocols based on established treatment guidelines (%)</th>
<th>Total no. off-label protocols based on primary research reports (Phase III or lower) (%)</th>
<th>No. off-label protocols with no evidence for their indication (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>68</td>
<td>10 (14.7)</td>
<td>10 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CNS</td>
<td>15</td>
<td>11 (66.7)</td>
<td>7 (63.6)</td>
<td>4 (36.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>22</td>
<td>8 (36.4)</td>
<td>7 (87.5)</td>
<td>1 (12.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>GI</td>
<td>60</td>
<td>32 (53.3)</td>
<td>23 (71.9)</td>
<td>3 (9.4)</td>
<td>6 (18.7)</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>31</td>
<td>16 (51.6)</td>
<td>11 (68.8)</td>
<td>2 (12.5)</td>
<td>3 (18.7)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>32</td>
<td>25 (78.1)</td>
<td>24 (96)</td>
<td>1 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>35</td>
<td>25 (71.4)</td>
<td>4 (80)</td>
<td>1 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lung</td>
<td>25</td>
<td>14 (56)</td>
<td>14 (93.3)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>74</td>
<td>20 (27)</td>
<td>12 (60)</td>
<td>5 (25)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Mobilisation</td>
<td>2</td>
<td>2 (100)</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>18</td>
<td>7 (38.9)</td>
<td>4 (57.1)</td>
<td>1 (14.3)</td>
<td>2 (28.6)</td>
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<tr>
<td>Other</td>
<td>2</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>26</td>
<td>14 (53.9)</td>
<td>8 (57.1)</td>
<td>6 (42.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skin</td>
<td>19</td>
<td>12 (63.2)</td>
<td>7 (58.4)</td>
<td>1 (8.3)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Transplants</td>
<td>19</td>
<td>11 (57.9)</td>
<td>1 (9.1)</td>
<td>10 (90.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>448</strong></td>
<td><strong>189 (42.2)</strong></td>
<td><strong>132 (69.9)</strong></td>
<td><strong>39 (20.6)</strong></td>
<td><strong>18 (9.5)</strong></td>
</tr>
</tbody>
</table>

CNS, central nervous system; GI, gastrointestinal.

### Table 1
Summary of off-label protocols (by tumour stream) and the level of evidence to support their use

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(cheaper) chemotherapy drugs thus being used off-label and therefore unfunded by the PBS while many expensive novel therapies are licensed and reimbursed.

Lack of TGA approval of drugs can also cause issues when attempting to conduct multinational clinical trials in Australia. In head-to-head trials, the standard of care arm (comparator) may contain drugs or protocols that are widely used overseas but not licensed by the TGA for the specific indication being evaluated in the trial. There is a risk that in these situations, local ethics committees may not allow the trial to proceed because of the lack of TGA approval of the standard treatment arm.

PBS funding is related to a cost-benefit analysis and not necessarily directly related to TGA approval (although drugs must be TGA-approved before they may be considered for PBS listing). Furthermore, drugs that are only administered in the inpatient setting are not PBS-funded in public hospitals even if they are PBS-listed for that indication. In our centre, non-PBS-funded drugs must be approved for use by the Pharmacy and Therapeutics Advisory Committee (PTAC). This is a multidisciplinary committee that examines the clinical data and cost of medicines. The funding in such cases therefore needs to come from either the treating institution or the patient (from personal funds or occasionally private health insurance funds if insured). Ethically cancer patients should not be denied access to active agents in the treatment of their malignancy. On the other hand, in the era of limited health resources, funding bodies need to remain mindful of cost-effectiveness and issues of risk-benefit. This can result in the best available treatments not being made available because of the limited nature of public funds.

There were 18 protocols that had no available published evidence to support their use for the indication in which they were being used. It is possible that these protocols were being used on the basis of abstracts that were presented at conferences but were not published, case reports or discussions with key international opinion leaders (based on their own experience). These protocols tended to be used for rarer malignancies or in unusual circumstances of common malignancies.

There was an agreement with the medical streams (haematology and medical oncology) about which protocols could be entered into CHARM. Those that contained drugs not approved by the PTAC were clearly labelled as ‘Individual Patient Approval (IPA) required’ to indicate the processes that must be followed before a patient could be put onto that particular protocol. An IPA requires formal approval from the head of the relevant stream and notification in advance to the pharmacy department. All IPAs are tabulated and reported at the next PTAC meeting for noting and discussion if necessary.

There are several limitations to this study. All protocols analysed in this project were sourced from a cancer medicines management database at a single institution, and it is possible, but unlikely, that they may not reflect current clinical practice at other institutions. Protocols were only evaluated according to the pathways or diseases by which they were categorised in the computer database. This method does not account for prescribers who may use a protocol for a different, uncategorised indication. Some protocols had ambiguous indication categorisation (e.g. ‘Other GI’) that made determining whether the drugs used were being used in an off-label setting difficult. A clinical judgement was made in this small number of cases to identify the most likely indication of use. In addition, no assessment was made as to which protocols could be administered in the outpatient or same-day patient setting, as public hospitals cannot claim drugs administered to inpatients from the PBS. This difference in funding arrangements between inpatient and day/ outpatients can act as a barrier to the appropriate use of drugs in cancer patients.

**Conclusion**

Our study found that over 90% of off-label protocols used in cancer patients were supported by established clinical guidelines and/or peer-reviewed research publications. Our study demonstrates that, despite the existence of such a high level of evidence, many cancer treatments are not TGA-approved. This results in a lack of PBS-reimbursed treatment options for cancer patients and may potentially impact on the success of their cancer therapy and thus survival.

Moving forward, it is imperative that professional groups work with key policymakers to develop a framework for a rapid and logical oncology drug approval mechanism outside of the standard TGA process to prevent the process lagging behind the clinical evidence and remove a potential barrier for patients accessing anticancer drugs.

**References**


Positive spillover effects of prescribing requirements: increased cardiac testing in patients treated with trastuzumab for HER2+ metastatic breast cancer


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Key words
breast cancer, trastuzumab, cardiotoxicity, drug safety, data linkage.

Abstract

Background: Cardiotoxicity is a concern in patients on trastuzumab therapy, and cardiac function assessment is a recommended practice. In 2006, trastuzumab was publicly subsidised for human epidermal growth factor receptor-2 early stage breast cancer with a requirement for cardiac testing prior to and during treatment.

Aim: To investigate the spillover effects of this requirement on testing rates in metastatic patients treated with trastuzumab where no monitoring requirements are applied.

Methods: We examined cardiac testing (echocardiography or multiple-gated acquisition scan) in 3779 women with metastatic breast cancer receiving trastuzumab between December 2001 and February 2010 and used interrupted time-series analyses to estimate changes in testing rates. The main outcome measures were the proportion of eligible patients, by quarter, receiving a cardiac function test pretreatment and during trastuzumab therapy.

Results: Only 21% of women had a cardiac function test pretreatment, and 47% were tested at some point during the first year of trastuzumab therapy. The introduction of mandatory cardiac testing for early breast cancer was associated with an immediate 8% increase (95% confidence interval, 2–14%) in pretreatment cardiac testing and an immediate 7% increase (95% confidence interval, 4–10%) in testing during therapy in metastatic patients. Testing rates during therapy increased steadily from early 2005, coinciding with the release of interim results from several trastuzumab trials reporting cardiac-safety outcomes.

Conclusion: The introduction of mandatory cardiac testing for early stage disease spilled over to the metastatic setting. While deviation from guidelines may be warranted in some cases, this study suggests underutilisation of cardiac testing among patients treated with trastuzumab in the metastatic setting.

Introduction

Breast cancer is the most common cancer in Australian women, representing more than a quarter of reported cancer cases.1 The disease has been managed by surgery, radiotherapy and systemic disease-modifying therapy: endocrine therapy and chemotherapy.2,3 In the last decade, the emergence of targeted therapies has provided new treatment options. The first of these targeted
therapies, trastuzumab, a recombinant monoclonal antibody, is now used routinely to treat human epidermal growth factor receptor-2 (HER2+) overexpressing early stage and metastatic breast cancer. In Australia, the drug has been publicly funded for patients with metastatic disease since 2001 through the Herceptin Program and for early stage disease since 2006 through the Pharmaceutical Benefits Scheme (PBS).

Trastuzumab is generally well tolerated. However, trastuzumab-mediated cardiotoxicity in metastatic breast cancer patients was demonstrated by retrospective analysis of the clinical trial data and single institutional case reviews. Subsequent adjuvant trastuzumab trials excluded individuals with pre-existing heart disease and incorporated strict schedules for cardiac function assessment. Despite these precautions, the trial data showed increased cardiac events in the trastuzumab-treated patients compared with the control arms. To address ongoing concerns about cardiotoxicity, clinical practice guidelines now recommend cardiac function assessment before commencing trastuzumab and during treatment. In accordance with these recommendations, when trastuzumab was listed on Australia’s PBS for treatment of early stage disease, the prescribing requirement stipulated that ‘cardiac function must be tested by a suitable method including, for example, echocardiogram or multiple gated acquisition, prior to seeking the initial authority approval and then at 3 monthly intervals during treatment’. Prescribers are required to declare in writing that the patient has had cardiac testing and does not have cardiac dysfunction and/or symptomatic heart failure. No such requirements are in place for patients receiving trastuzumab through the Herceptin Program.

There has been little research to date examining real-world use and outcomes of trastuzumab at a population level and even fewer studying processes of care (e.g. rates of cardiac testing) and patient outcomes. Notably, our previous research evaluating the first 4 years of Australia’s Herceptin Program found only 11% of metastatic breast cancer patients received cardiac function testing pretreatment, 26% at least once during the first course of trastuzumab therapy, and only 3% both before and during therapy.

We hypothesised that the prescribing requirement mandating cardiac function assessment in the adjuvant setting would influence cardiac testing rates among patients receiving trastuzumab for metastatic disease through the Herceptin Program, a phenomenon known as the ‘spillover effect’.

Methods

Setting and study population

The Herceptin Program is a national tax-payer-funded scheme that is outside the PBS. The programme was established in December 2001 after the Pharmaceutical Benefits Advisory Committee did not consider trastuzumab cost-effective for the treatment of HER2+ metastatic breast cancer. Patients who show evidence of HER2 overexpression are eligible for the programme. Herceptin Program enrollees are eligible for other PBS-listed medicines and for medical services covered by the Medicare Benefits Scheme (MBS). Our study cohort included all women enrolled in the Herceptin Program from December 2001 (the programme’s inception) to February 2010.

Data sources

De-identified data were obtained from Medicare Australia, the administering body of the Herceptin Program, PBS and MBS. To protect patient confidentiality, Medicare Australia extracted data from the Herceptin Program database and created a unique scrambled identifier for each enrollee, which was assigned to the enrollee’s MBS records. Medicare Australia provided the research team with two separate files: the Herceptin Program enrolment data (including age at the time of trastuzumab initiation) and MBS claims history. Cardiac function tests covered by the MBS were echocardiography (ECHO; MBS item codes 55113-55115) and multiple-gated acquisition (MUGA) scans (MBS item code 61313). Test results were not available from claims data, thus patients’ cardiac function levels could not be assessed using this data set.

MBS data were the sole data source used in this study to ascertain the number of cardiac tests performed on patients receiving trastuzumab. Cardiac testing could also be billed outside the MBS (through non-privatised hospital clinics) or when tests are fully funded by patients. As such, we attempted to estimate the extent to which MBS captures cardiac testing in cancer patients using data from cancer patients enrolled in a longitudinal cohort study examining the resource utilisation (including drugs prescribed, tests ordered, hospital, emergency department and doctor visits) and costs associated with drug treatment for breast, colorectal and lung cancer. Cancer patients were recruited from 11 treatment centres representing metropolitan, regional New South Wales and the public and private sector care. Participants consented to review of their medical charts and extracts of their secondary health data (including data from the MBS), which were subsequently linked to their primary data collection. Our analysis used data from 316 patients recruited...
to the cohort study in 2009 (observation period 14 January 2009 to 11 June 2010). We identified 129 scans (68 ECHO and 61 MUGA) in the medical chart review, 102 (79%) of which could be accounted for in the MBS data (i.e. tests recorded in the medical notes could be matched with an MBS record for the same type of test in the same period). ECHOs were captured at a slightly higher rate than MUGA scans (82% and 75% respectively).

Outcome measures and statistical analysis
Rates of pretreatment cardiac testing
We calculated the proportion of patients receiving cardiac function tests among new users of trastuzumab. Based on patients’ first-ever trastuzumab-dispensing record on the Herceptin Program, we identified the initiator population per quarter, which constituted the quarterly rolling denominator. The numerator was the total number of patients receiving a cardiac function test up to 60 days before the first dispensing of trastuzumab per quarter. To ensure that this look-back period was appropriate, we also performed a sensitivity analysis using the number of patients receiving cardiac testing up to 90 days pretreatment as the numerator.

Rates of cardiac testing during trastuzumab therapy
We defined a trastuzumab treatment episode as the period from the index trastuzumab dispensing to the last dispensing plus an additional 30 days (1-month supply of trastuzumab is standard practice). We calculated the proportion of patients receiving cardiac function tests among patients undergoing trastuzumab treatment. The treatment population per quarter was the rolling denominator with the total number of patients who received cardiac function tests during each quarter as the numerator. The quarterly proportion of patients receiving cardiac testing was chosen as an outcome measure because the PBS recommended testing at 3 monthly intervals. We conducted a sensitivity analysis where the proportion of patients receiving testing at 6 monthly intervals was used.

We first plotted quarterly measures to examine trends over the study period and used joinpoint regression analysis\textsuperscript{14} to identify segments within the time series and time points where there were statistically significant changes in trend. Apart from the October 2006 PBS requirement for regular cardiac testing, there was a joinpoint in the beginning of 2005 (March/April/May 2005), thus there were three segments from the quarterly measures of testing during trastuzumab therapy: from December 2001 to February 2005, from March 2005 to August 2006, and from September 2006 to February 2010. Next, we used segmented time-series models\textsuperscript{17} to determine the effect of the PBS requirement. This is a very strong analytical method for evaluating effects of an ‘interruption’ that occurs at a specific point in a time series.\textsuperscript{17–19} This method estimated the cohort-level changes in both the level and the trend of each outcome post-intervention, adjusting for the existing pre-intervention level and trend. We controlled for possible autocorrelation at the seasonal lag.\textsuperscript{17} All analyses were performed using SAS v9.2 (SAS Institute Inc., Cary, NC, USA). This study was approved by the St Vincent’s and Mater Health Sydney Human Research Ethics Committee (protocol H06/052) and the Medicare Australia External Request Evaluation Committee (2010/CO07329).

Results
There were 3779 women treated with trastuzumab for HER2+ metastatic breast cancer through the Herceptin Program between December 2001 and February 2010. Median age of the study cohort was 55 years (range 21–95).

Rates of pretreatment cardiac testing
Eight hundred and three (21.3%) women had cardiac function assessment up to 60 days before initiation of trastuzumab therapy. Figure 1 presents the quarterly rate of pretreatment cardiac-function testing. Prior to the introduction of mandatory cardiac testing for early breast cancer, on average, 15.4% of patients per quarter received testing, and testing increased at a rate of 0.4% per quarter (95% confidence interval (CI), 0.1–0.7; \( P = 0.01 \)). After the PBS prescribing requirement was implemented, we found an immediate 7.7% increase (95% CI, 1.8–13.7; \( P = 0.02 \)) in pretreatment testing rates without a significant change in trend. Our sensitivity analysis using a longer look-back period of 90 days demonstrated similar rates of cardiac testing.

Rates of cardiac testing during trastuzumab therapy
One thousand and twelve (26.8%) women had at least one cardiac function test during their first 3 months of trastuzumab therapy, 1489 (39.4%) during the first 6 months and 1791 (47.4%) at some point during the first year of therapy. Figure 2 illustrates the quarterly rate of cardiac-function assessment during trastuzumab therapy. Between December 2001 and February 2005, on average,
12.9% of patients per quarter received cardiac testing with no significant change in the trend. From early 2005, testing increased at a rate of 1.7% per quarter (95% CI, 1.3–2.1; \(P < 0.01\)). We observed an immediate 6.7% increase (95% CI, 3.7–9.8; \(P < 0.01\)) in testing rates after the introduction of mandatory cardiac testing for adjuvant treatment. Subsequently, testing continued to increase but at a lower rate of 0.6% per quarter (95% CI, 0.4–0.9; \(P < 0.01\)). The sensitivity analysis using the proportion of patients receiving cardiac testing on a half-yearly basis showed similar trends.

**Discussion**

Our longitudinal cohort study demonstrates a positive spillover effect of a prescribing requirement. Time-series analyses of trends in cardiac testing among patients with HER2+ metastatic breast cancer show immediate increases in testing both pretreatment and during therapy after the 2006 introduction of mandatory cardiac testing for early stage disease. Because prescribers are required to declare that patients’ cardiac function has been tested before commencing trastuzumab and during treatment in the adjuvant setting, not surprisingly, this behaviour of regular cardiac function assessment flowed on to metastatic breast cancer patients receiving trastuzumab. This and other research suggest requirements placed on prescribing can be a powerful tool in changing clinical practice.18–20 Carefully designed in accordance with the best evidence, they can help enhance quality use of medications. Clearly, there is a need for research to evaluate intended and unintended consequences of prescribing requirements on patterns of care and patient outcomes, particularly to detect unexpected adverse outcomes in a timely fashion.

We also observed a marked increase in testing rates during trastuzumab therapy from early 2005. This coincided with the release of interim analyses of phase III adjuvant trastuzumab trials showing increased cardiac incidents in the trastuzumab-treated patients compared.

*Figure 1* Proportion of metastatic breast cancer patients receiving a cardiac test before commencing trastuzumab therapy (from December 2001 to February 2010). PBS, Pharmaceutical Benefits Scheme.
with the control groups. The increase in testing observed in our study may reflect clinicians’ renewed concerns about trastuzumab’s cardiac safety in response to new data. Despite the increases seen in recent years, our study shows that only 21% of women had cardiac testing pretreatment, and less than half were tested during the first year of therapy. Trastuzumab-mediated symptomatic heart failure is rare (incidence of ~2%), and the cardiac damage is largely reversible. While clinicians and metastatic patients may place a lesser priority on monitoring the cardiac safety, our analysis suggests potential underuse of cardiac testing. Proactive management of cardiac health is recommended in patients treated with trastuzumab in both adjuvant and metastatic settings.

The major strengths of this study are the use of a large, nationwide cohort, longitudinal data (33 ‘real-world’ observation quarters over a 9-year period) and interrupted time-series analysis – one of the strongest quasi-experimental designs to examine changes following an intervention. Importantly, our post-marketing study of trastuzumab therapy and the current study investigating spillover impact of a prescribing requirement demonstrate the value of linkage of several health administrative databases. Privacy safeguards are important. However, privacy legislation should be modified in recognition of various mechanisms that can be used in data linkage to protect individual privacy and the potential benefits for our future healthcare through research that make best use of these data.

This study also has some limitations. First, this analysis was conducted using data from Medicare Australia, which has records of services provided in the community. Thus, we did not have information on cardiac tests performed on public inpatients or those fully self-funded by patients. However, there is no evidence to suggest an abrupt change in the recording of cardiac tests coinciding with the introduction of mandatory cardiac testing for early breast cancer. Therefore, while the actual testing rates over time might have been underestimated by MBS
statistics, the estimates of intervention impacts (level and trend changes) from the segmented regression models would not be affected by such underestimation. Further, based on a cohort study we are currently undertaking of New South Wales cancer patients and an observation period of 19 months, we found approximately 79% of cardiac tests recorded in their medical notes were captured by the MBS data. While this estimate may not necessarily apply to other states, there is no reason to expect substantial variability in MBS data capture by states. Moreover, we conducted a sensitivity analysis where we examined testing rates and trends by states. In larger states (New South Wales, Victoria and Queensland), where there were sufficient sample sizes, average testing rates were overall similar prior to the intervention. After the introduction of mandatory cardiac testing for early breast cancer, cardiac testing rates increased in all three states, and the increases did not differ substantially between states. Second, we had no information on patients’ clinical severity or well-being. It is likely that in some patients, regular cardiac testing as frequent as every 3 months is not clinically appropriate or necessary. Notwithstanding this limitation, the spillover effect of the PBS requirement remained apparent when we examined the rate of cardiac testing at 6 monthly intervals instead. Finally, this study only assessed processes of care and not cardiac safety of trastuzumab therapy, as claims data do not contain test results. Despite this, our findings are of merit in the clinical and policy domains.

Trastuzumab is an efficacious medication for treating HER2+ early stage and metastatic breast cancer, but cardiotoxicity is a rare but serious safety concern. We have demonstrated a positive spillover effect in cardiac monitoring rates among patients treated with trastuzumab for metastatic disease after the introduction of mandatory cardiac testing for adjuvant treatment. However, while deviation from guidelines may be warranted in some cases due to patient complexity and patient and/or clinician preferences, our findings indicates potential underutilisation of the recommended cardiac testing in metastatic breast cancer patients treated with trastuzumab.

Acknowledgements
We thank Medicare Australia for providing the data used for this study.

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Myelodysplastic syndrome in New Zealand and Australia

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Key words
myelodysplastic syndrome, epidemiology, haematology, New Zealand, Australia.

Abstract

Background: Myelodysplastic syndrome (MDS), a haematological disorder of the elderly, has been formally classified as a neoplastic disease for 10 years.

Aims: Our aim was to collate national cancer registry incidence data to describe the epidemiology of MDS in New Zealand.

Methods: The New Zealand Cancer Registry has now reported five complete years of incidence data, the last three of which were used for analysis. For the years 2005–2007, age–sex specific and age-standardised MDS incidence rates from New Zealand were compared with those from Australia. Age-standardised incidence rates were calculated by the direct standardisation method and standardised rate ratios were compared at the 5, 1 and 0.1% levels.

Results: Diagnoses of MDS represented 1.3% of total cancer registrations in New Zealand and 1.0% in Australia. In both New Zealand and Australia, 86–87% of MDS cases were diagnosed in individuals ≥60 years of age, the incidence increased significantly with age, and males had a significantly higher age-standardised incidence rate ($P < 0.001$) than females. The incidence rate for New Zealand males was significantly higher ($P < 0.001$) than Australian males. In both New Zealand males and females, the age-standardised incidence rate of MDS was significantly higher ($P < 0.05$) than most other haematological neoplasms.

Conclusions: In New Zealand and Australia, MDS is a common haematological neoplasm. The marked difference between male and female incidence rates, especially with advancing age, may provide insights into the causes of this disease.
Introduction

Myelodysplastic syndrome (MDS) is characterised by ineffective haemopoiesis, aberrant myeloid cell morphology, peripheral blood cytopenia, and a substantial risk of transformation to acute myeloid leukaemia (AML). Diagnosis of MDS is based on peripheral blood counts and morphology, together with morphological and cytogenetic analysis of bone marrow. Whereas MDS is extremely rare in childhood and adolescence, it is highly prevalent in elderly people. Approximately 80% of MDS patients are greater than 60 years of age at diagnosis and the incidence rate increases twofold for each decade over 40 years of age.

Reliable epidemiological data are lacking because of the characteristic heterogeneity of disease symptoms, its under-recognition by health professionals, inconsistent diagnostic practices, and changes in classification systems. Prior to 1976, MDS had a spectrum of various names and definitions, which led to the development of a classification system by the French–American–British (FAB) cooperative group, and subsequently by the World Health Organization (WHO). In 2001, the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) introduced MDS as a neoplastic disease whereas it was not included in previous editions.

Before ICD-O-3, the incidence of MDS was not typically recorded on population-based cancer registries; therefore epidemiological data for MDS are relatively immature worldwide. The available population-based data for several countries indicate that most patients are 60 years of age or older at diagnosis, the median incidence rate is four to five cases per 100,000, and males typically have a higher incidence rate than females. The small number of studies and the large variation in incidence rates between them emphasise the need for more population-based analyses of MDS.

Methods

The New Zealand Cancer Registry (NZCR) was accessed through the Ministry of Health’s website to obtain data on the age–sex specific incidence of MDS in New Zealand for the years 2005–2007. The NZCR is a population-based register of primary cancers diagnosed in New Zealand. During the time period mentioned earlier 65% of diagnoses were sourced from the National Minimum Dataset (NMDS), a national collection of public and private hospital discharge information for inpatients and day patients. Diagnostic laboratories supplied 32% of the diagnoses and 3% were sourced from death certificates. Cancers were registered once (in the year of their first known diagnosis) and classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Third Edition, MDS is coded in the range D46.0–D46.9. Registrations under this code, and all rates discussed in this paper, did not include chronic myelomonocytic leukaemia (CMML; C94.7). Since 2001 New Zealand and Australian laboratories have been coding MDS using WHO criteria in which cases with >20% blood or marrow blasts are excluded and classified as AML. MDS has been included in the NZCR registry since 2003, but the number of registrations in the first 2 years (140 and 384, respectively) was considerably different than those for 2005–2007 (see Supporting Information Table S1), presumably because of factors related to the initiation of data collection. Therefore, only these last 3 years of available data are included here. The NZCR also includes MDS mortality data, which are based on information provided by death certificates, postmortem reports, and death registration forms. Analysis of mortality rates is included as Supporting Information.

Under the Ministry of Health ethnicity data protocols, ethnicity information was collected primarily through self-identification. Each individual was allocated to a single ethnic group on the basis of the following priority: Māori; Pacific peoples; Asian; other groups except New Zealand European; and New Zealand European. Therefore, an individual who selected Māori as one of their three ethnicities was registered as Māori in the NZCR. For the purpose of this analysis, age–sex specific incidence of MDS in Māori was compared with the combined total of non-Māori New Zealand ethnic groups.

For comparison with the NZCR data, the Australian Cancer Incidence and Mortality (ACIM) workbooks were accessed through the Australian Institute of Health and Welfare website for the years 2005–2007. Similar to the NZCR, the ACIM workbooks provide a population-based summary of all cancer diagnoses and mortalities in Australia.

The age-specific MDS rates indicate the number of registrations per 100,000 of the estimated population in each age group for each year. Age-standardised incidence rates (for all ages) and truncated age-standardised incidence rates (for individuals aged 60 years) were calculated by the direct standardisation method, using the WHO standard world population. Standard errors of age-standardised rates were calculated by binomial approximation and used to determine 95% confidence intervals (95% CI). Comparisons of age-standardised rates were calculated by the direct method, comparing standardised rate ratios at the 5%, 1%, and 0.1% levels.
Results

There were 749 cases (462 males, 287 females) of MDS diagnosed in New Zealand between 2005 and 2007 (Supporting Information Table S1), representing 1.5% of cancer registrations in males and 1.1% in females. For both males and females, 87% of MDS cases were diagnosed in individuals aged ≥60 years (median age at diagnosis = 77 years) and the incidence of MDS increased with age (Fig. 1a). In comparison, there were 3367 cases of MDS diagnosed in Australia between 2005 and 2007 (Supporting Information Table S1), representing 1.1% of cancer registrations in males and 1.0% in females. Similar to New Zealand data, 86% of MDS cases were diagnosed in individuals aged ≥60 years (median age = 78 years for males, 79 years for females) (Fig. 1b). Age-specific rates of MDS were similar between New Zealand and Australian females, but across most age groups the reported rate of MDS was higher in New Zealand males than Australian males ($P < 0.001$; Fig. 1c,d). Table 1 shows a summary of age standardised incidence rates for all ages and truncated age-standardised rates for individuals aged ≥60 years.

In both New Zealand and Australia, the age-standardised incidence rates of MDS were significantly higher in males than females ($P < 0.001$, Fig. 1d). From the age of 60 years the sex ratios (male to female) of MDS incidence rates increase (Fig. 2). In New Zealanders aged 60–69 years, 70–79 years, and 80 years the sex ratios were 1.3, 2.2 and 2.8 respectively. Similarly the sex ratios for these age groups in Australians were 1.5, 2.1 and 2.3 respectively. New Zealand males had an age-standardised rate of 5.4 per 100 000 per year with a 95% confidence interval of 4.9 to 5.9 per 100 000 per year, 2.1-fold higher than the female rate of 2.6 (95% CI 2.3–2.9). The combined age-standardised rate for New Zealand males and

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Figure 1  Incidence of MDS in New Zealand (NZ) and Australia (AUS). In both males and females from New Zealand (a) and Australia (b), the majority of MDS cases were diagnosed in individuals aged ≥60 years and the incidence of MDS increased with age. (c) Across most age groups the rate of MDS was higher in New Zealand males than Australian males. (d) In both New Zealand and Australia, the age-standardised incidence rate of MDS was significantly higher (***$P < 0.001$) in males than females. The rate for New Zealand males was significantly higher (***$P < 0.001$) than Australian males.

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females was 3.7 (95% CI 3.5–4.0). The rate for Australian males was 4.3 (95% CI 4.1–4.5), 1.9-fold higher than the female rate of 2.3 (95% CI 2.2–2.4). The combined age-standardised rate for Australian males and females was 3.2 (95% CI 3.1–3.3). The truncated age-standardised rate for New Zealand males aged ≥60 was 41.5 (95% CI 40.1–42.9), 2.2-fold higher than the female rate of 19.2 per 100 000 per year (95% CI 18.4–20.1) (P < 0.001). The rate for Australian males aged ≥60 was 32.6 (95% CI 32.1–33.1), 2.0-fold higher than the female rate of 16.0 (95% CI 15.7–16.4) (P < 0.001).

Between 2005 and 2007, Māori comprised 15.1% of the New Zealand population for both males and females. There were 44 diagnoses (26 males, 18 females) of MDS per 100 000 per year, World Health Organization standard world population. ±95% confidence intervals (95% CI) calculated by binomial approximation.

Table 1 Age standardised incidence rates of myelodysplastic syndrome in New Zealand and Australia, 2005–2007

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New Zealand</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male Māori</td>
<td>5.4</td>
<td>2.6</td>
<td>3.7</td>
<td>41.5</td>
<td>19.2</td>
<td>28.3</td>
</tr>
<tr>
<td>Female Māori</td>
<td>6.6</td>
<td>3.6</td>
<td>4.9</td>
<td>53.2</td>
<td>27.6</td>
<td>40.8</td>
</tr>
<tr>
<td>Non-Māori</td>
<td>5.3</td>
<td>2.6</td>
<td>3.7</td>
<td>40.8</td>
<td>18.8</td>
<td>28.3</td>
</tr>
<tr>
<td>Australia</td>
<td>4.3</td>
<td>2.3</td>
<td>3.2</td>
<td>32.6</td>
<td>16.0</td>
<td>23.1</td>
</tr>
</tbody>
</table>

†Age-standardised incidence rate (ASR) and truncated age-standardised rate (TASR), per 100 000 per year, World Health Organization standard world population. ‡95% confidence intervals (95% CI) calculated by binomial approximation.
in New Zealand Māori between 2005 and 2007 (Supporting Information Table S2), representing 1.2% of cancer registrations in Māori males and 0.7% in females. For males, approximately 88% of MDS cases were diagnosed in individuals aged ≥60 years (median age at diagnosis = 74 years), whereas 77% of MDS cases were diagnosed in females aged ≥60 years (median age at diagnosis = 72 years).

Table 1 shows a summary of age-standardised incidence rates for Māori and non-Māori of all ages and truncated age-standardised rates for individuals aged ≥60 years. Whereas the age-standardised rate for non-Māori males was significantly higher than non-Māori females ($P < 0.001$), there was no significance difference between age-standardised incidence rates of male and female Māori. There was also no significant difference between Māori and non-Māori across all ages. However, the truncated age-standardised incidence rates for Māori aged ≥60 were significantly higher than non-Māori in both males ($P < 0.01$) and females ($P < 0.001$). The age-standardised rate for Māori males was 6.6 (95% CI 4.0–9.3) and the rate for females was 3.6 (95% CI 1.9–5.2). The combined age-standardised rate for Māori males and females was 4.9 (95% CI 3.4–6.4). The age-standardised rate for non-Māori males was 5.3 (95% CI 4.8–5.8) and the rate for females was 2.6 (95% CI 2.2–2.9).

The age-standardised incidence rates of MDS in males and females (5.4 and 2.6 per 100 000 per year respectively) were compared with other common haematological neoplasms. Of those analysed, diffuse non-Hodgkin lymphoma (diffuse NHL) had a significantly higher ($P < 0.001$) incidence rate in New Zealand males (7.6) and females (5.3) and plasma cell myeloma had a significantly higher ($P < 0.05$) incidence rate in females (3.2). The age-standardised incidence rates of all other analysed neoplasms (follicular NHL, T-cell NHL, chronic lymphocytic leukaemia, AML, polycythaemia vera and essential thrombocythaemia) were either similar to or significantly lower ($P < 0.05$) than that of MDS.

### Discussion

This paper provides an analysis of recent population-based MDS incidence data from New Zealand and Australia. MDS has had a low profile in national cancer registries because of its relatively late recognition as a bona fide cancer, confusion over nomenclature and classification, and its under-recognition by health professionals. MDS has been formally classified as a neoplastic disease for 10 years and this is reflected by the relative immaturity of epidemiological data for most countries. Indeed, incidence data for MDS in New Zealand and Australia have only been included in their respective national cancer registries since 2003.

The New Zealand and Australian incidence rates are similar to those reported in previous studies. Table 2 provides a summary of the available population-based MDS

### Table 2 Review of reported data on myelodysplastic syndrome in population-based studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Period of study</th>
<th>Population in study</th>
<th>Incidence rate (per 100 000)</th>
<th>Median age at diagnosis</th>
<th>Sex ratio (male : female)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden (Jönköping)</td>
<td>1978–1992</td>
<td>310 000</td>
<td>3.6</td>
<td>76</td>
<td>—</td>
<td>Rådlund et al.</td>
</tr>
<tr>
<td>UK (Bournemouth)</td>
<td>1981–1990</td>
<td>220 000</td>
<td>12.6</td>
<td>73</td>
<td>0.9</td>
<td>Williamson et al.</td>
</tr>
<tr>
<td>Germany (Düsseldorf)</td>
<td>1986–1990</td>
<td>580 000</td>
<td>4.1</td>
<td>71</td>
<td>1.2</td>
<td>Aul et al.</td>
</tr>
<tr>
<td>UK (England/Wales)</td>
<td>1984–1993</td>
<td>16 000 000</td>
<td>4.0</td>
<td>—</td>
<td>1.2</td>
<td>Cartwright et al.</td>
</tr>
<tr>
<td>UK (Somerset)</td>
<td>1985–1993</td>
<td>410 000</td>
<td>9.3</td>
<td>—</td>
<td>—</td>
<td>Phillips et al.</td>
</tr>
<tr>
<td>France (Côte-d’Or)</td>
<td>1980–2004</td>
<td>490 000</td>
<td>1.3</td>
<td>75</td>
<td>2.0</td>
<td>Maynardie et al.</td>
</tr>
<tr>
<td>France (Basque)</td>
<td>1993–1996</td>
<td>290 000</td>
<td>7.7</td>
<td>74</td>
<td>1.0</td>
<td>Bauduer et al.</td>
</tr>
<tr>
<td>Germany (Düsseldorf)</td>
<td>1991–2001</td>
<td>580 000</td>
<td>4.9</td>
<td>72</td>
<td>1.3</td>
<td>Gering et al.</td>
</tr>
<tr>
<td>Spain (Ourense)</td>
<td>1994–1998</td>
<td>350 000</td>
<td>8.1</td>
<td>78</td>
<td>1.3</td>
<td>Iglesias Gallego et al.</td>
</tr>
<tr>
<td>Spain (Aragon)</td>
<td>1998</td>
<td>1 180 000</td>
<td>2.8</td>
<td>74</td>
<td>2.0</td>
<td>Giralt et al.</td>
</tr>
<tr>
<td>UK (South Thames)</td>
<td>1999–2000</td>
<td>5 500 000</td>
<td>3.5</td>
<td>77</td>
<td>1.6</td>
<td>Phekoo et al.</td>
</tr>
<tr>
<td>Germany (Düsseldorf)</td>
<td>1996–2005</td>
<td>580 000</td>
<td>2.5</td>
<td>73</td>
<td>1.8</td>
<td>Neukirchen et al.</td>
</tr>
<tr>
<td>USA (SEER)</td>
<td>2001–2003</td>
<td>76 000 000</td>
<td>3.4</td>
<td>76</td>
<td>1.7</td>
<td>Ma et al.</td>
</tr>
<tr>
<td>USA (NAACCR)</td>
<td>2001–2003</td>
<td>240 000 000</td>
<td>3.3</td>
<td>76</td>
<td>1.8</td>
<td>Rollinson et al.</td>
</tr>
<tr>
<td>New Zealand (Wellington)</td>
<td>2002–2007</td>
<td>450 000</td>
<td>2.8</td>
<td>70</td>
<td>1.5</td>
<td>Irwin et al.</td>
</tr>
<tr>
<td>New Zealand (NZCR)</td>
<td>2005–2007</td>
<td>4 200 000</td>
<td>3.7</td>
<td>77</td>
<td>2.1</td>
<td>Present study</td>
</tr>
<tr>
<td>Australia (ACIM)</td>
<td>2005–2007</td>
<td>21 000 000</td>
<td>3.2</td>
<td>78</td>
<td>1.9</td>
<td>Present study</td>
</tr>
</tbody>
</table>

†Age-standardised incidence rates (per 100 000). ‡Studies listed in order of study period midpoint. §Estimated catchment area population over period of study. ¶Sex ratio calculated by dividing male incidence rates by female incidence rate. NAACCR, North American Association of Central Cancer Registries; SEER, Surveillance, Epidemiology, and End Results.
data for several countries. Within this small group of studies, there is large variation in incidence rates that range from 1.3 to 12.6 per 100 000 per year. The two studies with the highest incidence rates were small studies from catchment areas where >22% of residents were older than 65, considerably higher than the national average.14,17 The most recent Surveillance, Epidemiology and End Results3 and North American Association of Central Cancer Registries4 studies from the United States, which are the largest population-based MDS studies to date show age-standardised rates (3.4 and 3.3 per 100 000) that are very similar to those in this study.

Registry- and population-based studies are limited by the accuracy and completeness of case notification. Because of this and because there have been no formal studies of the rate of case notification to the NZCR or ACIM, we hesitate to place any significance on the slightly higher rate of MDS in New Zealand than Australia, or on the different rates identified in other countries, such as Thailand (56),31 Central Africa (57),32 Korea (57),33 Turkey (61)34 and Romania (62),35 for incidence difference between sexes is unknown, but ratio (male to female) ranges from 0.9 to 2.0. The reason for incidence difference between males and females, they do not explain why the sex ratios increase with age, as shown in this and previous studies.5,16 In New Zealanders aged 60–69 years, 70–79 years and 80 years the sex ratios were 1.3, 2.2, and 2.8 respectively. Similarly, the sex ratios for these age groups in Australians were 1.5, 2.1, and 2.3 respectively. A male preponderance occurs in many haematological malignancies in all age groups, including childhood.16 This consistent sex bias suggests that haemopoiesis could be more ‘vulnerable’ in males than in females, and perhaps the focus on environmental exposures is over-emphasised. Telomere length, which is reduced in patients with MDS,43 provides a possible marker of biological age. Consistent with the sex disparity in MDS cases, it is interesting that blood cells in males have shorter telomeres than females.44 Additional study of the relationship between telomere length, sex and MDS would be useful.

Conclusion

The data in this paper provide a snapshot of MDS incidence in New Zealand and Australia. Future analyses in these countries would benefit from longer study periods, a review of completeness of case ascertainment, MDS subtype classification, and mortality rates. As the population ages, MDS will contribute increasingly to the health burden, especially for males. The marked difference between male and female sex incidence rates, especially with advancing age, may provide a key element in our understanding of this disease.

Acknowledgements

The authors would like to acknowledge NZCR and ACIM registry staff for providing incidence data and Dr Hilary Blacklock, Department of Haematology, Middlemore Hospital, Counties Manukau District Health Board, for helpful comments on the paper.
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**Supporting information**

Additional Supporting Information may be found in the online version of this article:

**Figure S1** Mortality rates of MDS in New Zealand (NZ) and Australia (AUS). In both males and females from New Zealand (a) and Australia (b), the majority of MDS mortalities were of individuals aged ≥60 years (c) Across most age groups the mortality rate of MDS was similar between New Zealand and Australian persons. (d) In both New Zealand and Australia, the age-standardised mortality rate of MDS was significantly higher (**P < 0.001) in males than females.

**Figure S2** Sex ratio (male to female) of MDS mortality in New Zealand (NZ) and Australia (AUS). In both New Zealand (a) and Australia (b), the mortality rate of MDS across most age groups was higher in males than females and from the age of 60 years the sex ratio increases.

**Table S1** Age–sex specific incidence of myelodysplastic syndrome in New Zealand and Australia (2005–2007).

**Table S2** Age–sex specific incidence of myelodysplastic syndrome in New Zealand Māori and non-Māori (2005–2007).
How we use recombinant activated Factor VII in patients with haemophilia A or B complicated by inhibitors

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Key words
inhibitor, haemophilia A, haemophilia B, NovoSeven, recombinant activated Factor VII.

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Introduction
Approximately 10–30% of patients with haemophilia A and 1–5% of those with haemophilia B develop inhibitors against infused coagulation factors.1–3 Up to 60% of Factor VIII (FVIII) inhibitors are low titre (<10 BU/mL), and as many as 50% are transient, disappearing with continued exposure to infused FVIII.4 For those individuals with persistently high titre inhibitors, a major consideration is the management of bleeds.5 Recombinant activated Factor VII (rFVIIa; NovoSeven RT) is an established therapy in these patients. To develop a consensus-based guide on the practical usage of rFVIIa in haemophilia complicated by inhibitors, nine expert haemophilia specialists from Australia and New Zealand developed practice points on the usage of rFVIIa, based on their experience and supported by published data. Practice points were developed for 13 key topics: control of acute bleeding; prophylaxis; surgical prophylaxis; control of breakthrough bleeding during surgery or treatment of acute bleeds; paediatric use; use in elderly; intracranial haemorrhage; immune tolerance induction; difficult bleeds; clinical monitoring of therapy; laboratory monitoring of therapy; concomitant antifibrinolytic medication; practical dosing. Access to home therapy with rFVIIa is important in allowing patients to administer treatment early in bleed management. In adults, 90–120 µg/kg is the favoured starting dose in most settings. Initial dosing using 90–180 µg/kg is recommended for children due to the effect of age on the pharmacokinetics of rFVIIa. In the management of acute bleeds, 2-hourly dosing is appropriate until bleeding is controlled, with concomitant antifibrinolytic medication unless contraindicated. The practice points provide guidance on the usage of rFVIIa for all clinicians involved in the management of haemophilia complicated by inhibitors.

Abstract
The management of bleeds in patients with haemophilia A or B complicated by inhibitors is complex. Recombinant activated Factor VII (rFVIIa; NovoSeven RT) is an established therapy in these patients. To develop a consensus-based guide on the practical usage of rFVIIa in haemophilia complicated by inhibitors, nine expert haemophilia specialists from Australia and New Zealand developed practice points on the usage of rFVIIa, based on their experience and supported by published data. Practice points were developed for 13 key topics: control of acute bleeding; prophylaxis; surgical prophylaxis; control of breakthrough bleeding during surgery or treatment of acute bleeds; paediatric use; use in elderly; intracranial haemorrhage; immune tolerance induction; difficult bleeds; clinical monitoring of therapy; laboratory monitoring of therapy; concomitant antifibrinolytic medication; practical dosing. Access to home therapy with rFVIIa is important in allowing patients to administer treatment early in bleed management. In adults, 90–120 µg/kg is the favoured starting dose in most settings. Initial dosing using 90–180 µg/kg is recommended for children due to the effect of age on the pharmacokinetics of rFVIIa. In the management of acute bleeds, 2-hourly dosing is appropriate until bleeding is controlled, with concomitant antifibrinolytic medication unless contraindicated. The practice points provide guidance on the usage of rFVIIa for all clinicians involved in the management of haemophilia complicated by inhibitors.
(NovoSeven RT, Novo Nordisk) has been developed to allow for fast, early treatment in both the home and hospital settings, and to provide added convenience and treatment flexibility. The formulation, which is bioequivalent to the first-generation product, remains stable for 24 months when stored at 25°C and for 6 months when stored at 40°C.

This document aims to provide a practical guide for using rFVIIa in patients with haemophilia with inhibitors, relevant to Australia and New Zealand. It is meant to be used in the context of collaboration with an experienced haemophilia physician. Health economics studies of rFVIIa in patients with inhibitors conducted in Australia, Europe and the USA suggest long-term cost-effectiveness and improved health-related quality of life with treatment. Nevertheless, the cost of haemophilia care is high, especially for patients with inhibitors, and the panel has endeavoured to be realistic in its recommendations.

Materials and methods

Expert group

The expert author group comprises experienced haematologists from Australia and New Zealand. Group members were selected based on demonstrated expertise in haemophilia, an interest in development of a practical usage guide of rFVIIa, geographical representation from both Australia and New Zealand, and diversity in views and expertise (including experts in paediatric and adult haemophilia care, and surgery). The group was chaired by Dr Simon Brown.

Practice points

The expert group met in Melbourne in April 2011. The meeting agenda was driven by 13 topics that were identified as being key to the practical usage of rFVIIa in patients with inhibitors. Two working groups were formed based on specific areas of expertise. The working groups developed practice points for individual topics, based on collective experience and the published medical literature. These were then considered by the full panel. Document development involved discussion and consultation by email and telephone. A group teleconference call was held in September 2011 to review, discuss and finalise the manuscript. The practice points represent a consensus of the views of the group members, on the use of rFVIIa for inhibitor management. They are not based on or meant to reflect funding of rFVIIa in individual countries, nor to override local guidelines.

Results

Aims of treatment with rFVIIa

The primary aim of treatment with rFVIIa is to achieve haemostasis during bleeding episodes and to prevent bleeding episodes. Secondary aims are to increase patients’ quality of life by reducing pain, maintaining functionality and improving quality of life by easy access to home treatment. Practice points were developed under 13 key topics which contribute to achieving these aims. Each practice point has the consensus of all members of the expert group.

Control of acute bleeding

Practice points

- Adult starting dose: 90–120 µg/kg
- Paediatric starting dose: 90–180 µg/kg
- Dosing at 2-hourly intervals until haemostasis is achieved (total number of doses depends on nature and site of bleed)
- A single high dose is an alternative to repeated standard dosing in selected patients
- If initial response following first dose is inadequate, consider a higher dose
- Once haemostasis is achieved, follow-up dosing may be reduced to a standard 90 µg/kg
- Concomitant antifibrinolytic therapy is encouraged (see section on ‘Concomitant medications’)  
- Involve a haemophilia specialist early

Early intervention with rFVIIa is effective in the treatment of muscle, mucocutaneous and mild to moderate joint bleeds; early intervention in joint bleeds can minimise joint damage and reduce the need for orthopaedic surgery. Starting doses of rFVIIa ranged from 35 µg/kg to 270 µg/kg in 11 studies of on-demand treatment of joint bleeds included in a systematic review. The most commonly utilised initial dose was 90 µg/kg, and dosage intervals ranged from 2-hourly to 3-hourly. The approved dose in Australia and New Zealand is 35–120 µg/kg at 2–3-hourly intervals until control of bleeding is achieved, then 3–12-hourly if continued treatment is necessary. Based on clinical data, 2–3 injections of 90 µg/kg or one single injection of 270 µg/kg can be recommended. New Zealand guidelines recommend that a dose of 90 µg/kg be given 2-hourly initially, with the frequency reduced to 3-hourly and then 4-hourly as indicated by clinical progress until bleeding ceases. Pharmacokinetic studies indicate that higher doses may be required in children, as rFVIIa plasma clearance is higher in the paediatric age group: in a study that included 12 children (2–12 years) and 6 adults (18–55 years).
years), the total body clearance of rFVIIa normalised for bodyweight was significantly higher in children (78 mL/kg/h, vs 53 mL/kg/h for adults; \( P < 0.05 \)).28

Results from three randomised clinical trials in patients aged 1–50 years show that a single dose of 270 \( \mu g/kg \) is at least as efficacious and safe as three doses of 90 \( \mu g/kg \) each.29–31 In another study, a single dose of 150 \( \mu g/kg \) stopped mild-to-moderate bleeding in 37.5% of bleeding episodes in adults, with haemostasis being achieved in the remaining 62.5% of bleeding episodes after a second dose of 90 \( \mu g/kg \).32 Data from the Haemophilia and Thrombosis Research Society (HTRS) Registry also showed significantly increased efficacy with doses above 200 \( \mu g/kg \), compared with doses below 200 \( \mu g/kg \) (97% vs 84%; \( P < 0.001 \)), suggesting that a single high-dose injection is an alternative to repeat standard dosing.33 Evidence for the safety of higher doses was provided by an HTRS Registry data analysis of 172 bleeds in patients with a median age of 6.5 years (range: 0.4–41.7 years) treated with rFVIIa 250 \( \mu g/kg \) or higher, with no serious adverse drug-related events or thrombotic complications being reported.34

Prophylaxis

Practice points

- **Starting dose:** 90 \( \mu g/kg \) once-daily
- **Increase or decrease dose and/or frequency, depending on response**
- **Monitor bleeds and symptoms (clinical review and patient diaries)**
- **Continue or limit prophylaxis, depending on indication and response**

The panel believes that prophylaxis is beneficial in patients with haemophilia complicated by inhibitors. Close monitoring of patients on prophylaxis is critical to determine efficacy. As well as being clinically monitored, patients should keep a bleeding event record that can be assessed by their haemophilia treatment team. Duration of prophylactic therapy depends on bleeding response and the indication for the prophylaxis; it may take 2–3 months to assess effect. Once the synovial inflammation in a target joint has settled, the requirement for ongoing prophylactic therapy should be reassessed.

Prophylactic treatment in patients with haemophilia A or B helps to significantly bleeding reduce episode frequency, prevent joint damage and improve health-related quality of life.35–41 Patients with haemophilia A or B with inhibitors and a high bleeding frequency (defined as four or more bleeding episodes per month) can be treated with rFVIIa administered as a once-daily dose of 90 \( \mu g/kg \) for up to 3 months to reduce the frequency of bleeding, consistent with the Australian and New Zealand approved dosing.8 The efficacy of this regimen has been confirmed in a clinical trial of 22 patients aged 5–51 years randomised to receive 90 \( \mu g/kg \) or 270 \( \mu g/kg \) rFVIIa for 3 months.42 Descriptive patient case histories also suggest a beneficial effect with rFVIIa administration 2–3 times per week.43,44

Clinical experience suggests that the haemostatic action of rFVIIa exceeds its predicted half-life.45 Several potential mechanisms have been postulated for this effect. Sustained low levels of rFVIIa circulating in the body may reduce inflammatory synovitis.42,45,46 rFVIIa may also be internalised into platelets and redistributed into sub-endothelial compartments.47 In vitro studies support the diffusion of rFVIIa into the extravascular space, where it forms complexes with tissue factor and facilitates thrombin generation on platelets, thereby plugging leaks in small blood vessels.35–49 It is possible that more than one of the proposed mechanisms has a part to play in the prolonged prophylactic action of rFVIIa.

Surgical prophylaxis

Practice points

- **Adult starting dose:** 90–120 \( \mu g/kg \)
- **Paediatric starting dose:** 90–180 \( \mu g/kg \)
- **Follow immediately with 90 \( \mu g/kg \) 2-hourly**
- **Major surgery (e.g. orthopaedics, cranial): 2-hourly dosing for \( \geq 4–5 \) days, then 3–6-hourly for up to 12 days**
- **Antifibrinolytic agents are safe during surgery (see section on ‘Concomitant medications’ below)**
- **Intensive perioperative haemophilia team involvement is mandatory to identify factors that might increase bleeding risk**

High-level planning involving the surgeon, anaesthetist and the haemophilia team is essential. Due diligence needs to be followed with regard to dosing frequency and dosing intervals because of the risk of breakthrough bleeding in these patients when a dose is omitted.50 A consensus protocol for the use of rFVIIa in elective orthopaedic surgery in patients with inhibitors recommends a preoperative dosing of 120–180 \( \mu g/kg \) of rFVIIa, immediately followed by 90 \( \mu g/kg \) at 2-hourly intervals.50 The protocol recommends the concomitant administration of an antifibrinolytic agent (e.g. tranexamic acid), started the evening before surgery, unless there is a strong contraindication.50

The approved dose in Australia and New Zealand for surgical prophylaxis is 35–120 \( \mu g/kg \) 2–3-hourly for 1–2 days, then 2–6-hourly if continued treatment is necessary.8 The 35 \( \mu g/kg \) dose may not be adequate: data from a randomised clinical trial comparing rFVIIa 35 \( \mu g/kg \) and 90 \( \mu g/kg \) for elective surgery show that the 35 \( \mu g/kg \) dose is less effective at maintaining haemostasis.
following surgery. In that study, patients received rFVIIa (35 μg/kg, n = 15; 90 μg/kg, n = 14) 2-hourly for the first 48 h, then 2–6-hourly for the following 3 days. Satisfactory haemostasis was achieved during the first 48 h by 100% of patients receiving 90 μg/kg rFVIIa, compared with 80% of patients receiving 35 μg/kg rFVIIa (difference not significant). After 5 days, the proportion of patients with satisfactory haemostasis was 93% in the 90 μg/kg dose group, compared with only 60% in the 35 μg/kg group (P < 0.05).

Control of breakthrough bleeding during surgery or treatment of acute bleeds

Practice points
• Escalate dose and/or reduce dosing intervals to 2-hourly
• Add antifibrinolytic agent if not contraindicated and if not already in use
• Consider treatment change if no response or deterioration
rFVIIa has consistently demonstrated effectiveness in treatment of bleeding episodes in patients with congenital haemophilia A or B with inhibitors undergoing major or minor surgical procedures. In a randomised clinical trial, 90 μg/kg dosing was shown to be more effective than 35 μg/kg at maintaining late haemostasis following elective surgery.

Special populations: Paediatrics

Practice point
• Higher doses of rFVIIa may be required in paediatric patients
Higher doses of rFVIIa may be needed in children because of the higher rFVIIa plasma clearance in paediatric than in adult patients with haemophilia. The safety and efficacy of rFVIIa appear to be comparable in adult and paediatric patients when dosed on a bodyweight basis. Due to insufficient data in this patient population, a single 270 μg/kg dose in children under 18 years of age is not approved in either Australia or New Zealand.

Special populations: Elderly

Practice point
• Carefully consider elective procedures in elderly patients, based on their individual circumstances
Elderly patients are more likely to have a history of stroke and cardiac events, and are at increased risk of thrombosis. Elective procedures should be carefully considered in this patient population, based on individual circumstances. An appropriate dose in the elderly is 90 μg/kg.

Intracranial haemorrhage (ICH)

Practice points
• Adult starting dose: 90–120 μg/kg (2-hourly)
• Paediatric starting dose: 90–180 μg/kg (2-hourly)
• Continue treatment for up to 14 days
• Monitor patients closely
• If no response, see section on ‘Difficult bleeds’
• Seek neurosurgical/neurological advice early
• Prophylaxis post-ICH may be necessary

Findings from the rFVIIa emergency use programme suggest that rFVIIa is an effective and well-tolerated option in the management of ICH in patients with haemophilia complicated by inhibitors. A retrospective review of the HTRS database from 2004 to 2008 found standard dosing of rFVIIa to be safe and effective in treating ICH in patients with inhibitors. A review of current evidence supports prophylaxis following an ICH to prevent recurrence of the bleeding event.

Immune tolerance induction (ITI)

Practice points
• Use on-demand rFVIIa in newly diagnosed patients with inhibitors
• Consider secondary prophylaxis with rFVIIa after a bleed
The use of rFVIIa as secondary prophylaxis in haemophilia patients with inhibitors before and during ITI therapy, and after ITI failure to prevent joint bleeding and protect against joint damage, is an emerging treatment possibility. Treatment guidelines issued by the Australian Haemophilia Centre Directors’ Organisation (AHCDO) recommend that ITI should be considered in all patients with inhibitors to Factor VIII. The guidelines note that ITI for patients with haemophilia B and inhibitors to Factor IX is difficult. A review of current evidence supports prophylaxis with rFVIIa as the recommended bypassing agent during the pre-ITI period and ITI, for its ability to provide safety from anamnestic responses and safety from pathogen transmission. Once on ITI therapy, treatment with activated prothrombin complex concentrates (APCCs) may be contraindicated in patients with haemophilia B (but not in those with haemophilia A). If bleeding is life-threatening, APCCs may be necessary in some instances in patients with haemophilia B even if the ITI therapy is ongoing.
Difficult bleeds

Practice point

• Management of life- or limb-threatening bleeds must be in hospital under haemophilia specialist care

Difficult bleeds are defined as being a risk to life or limb and include re-bleeding during surgery. Early recognition of a bleeding episode is important. To reduce complications of further bleed development, treatment needs to be started as early as possible.23,25,60–62 For initial treatment of acute, severe bleeding episodes, compliance with a 2–3-hourly administration schedule is essential to maintain haemostasis.5,63,64 A consensus algorithm for the treatment of problem bleeds in patients with severe haemophilia A and inhibitors emphasises the importance of frequent evaluation of patient response to treatment and of optimising the timing of treatment decisions.65

Monitoring of rFVIIa therapy: clinical monitoring

Practice point

• The effectiveness of rFVIIa and the treatment regimen is assessed clinically

Current practice relies on clinical parameters to assess the effectiveness of rFVIIa and the treatment regimen used. Clinical effectiveness is judged based on parameters, such as swelling, pain, bruising, pallor, non-response to analgesics, restriction of motion and reduced mobility, compared with baseline, and the patient’s perception of ongoing bleeding.66 A consensus definition of non-responsive bleeding episodes in patients with haemophilia with inhibitors suggests that a non-responsive joint or muscle bleed can be defined as: persistence/worsening of pain, a patient’s perception of active bleeding and/or both an increase/persistence in swelling and a decrease in mobility.66 The timing of assessment should be left to the discretion of the physician, but a non-life- or limb-threatening joint or muscle bleed should be considered non-responsive to bypass treatment if the clinical scenario meets the criteria after 24–48 h of treatment. An accelerated time frame for assessment of response to treatment should be considered for life- and limb-threatening bleedings (e.g. ICH). Imaging techniques, such as ultrasound, computed tomography, X-ray or magnetic resonance imaging, may be suitable in the evaluation of muscle bleeds, but should be interpreted in the clinical context.66 Coagulation parameters and full blood count should be monitored for the development of consumptive coagulopathy.

Monitoring of rFVIIa therapy: laboratory monitoring

Practice point

• Laboratory monitoring is of limited value

Routine laboratory coagulation parameters have not been shown to correlate consistently with the degree of haemostasis obtained in patients receiving inhibitor therapy.66 Assays, such as thromboelastography and rotational thromboelastometry, have been used in the research setting but have not been validated for use in routine clinical practice.66–68 Preliminary data suggest that a standardised thrombin-generation assay may prove useful in individualising rFVIIa regimens.57

Concomitant medications

Practice point

• Antifibrinolytic agents may be administered concomitantly

Concomitant administration of an antifibrinolytic agent (e.g. tranexamic acid) is appropriate and may enhance the effect of rFVIIa.50,64,69–71 An overview of 53 orthopaedic surgical procedures using rFVIIa noted that antifibrinolytic agents were used in combination with rFVIIa in most cases.70 Antifibrinolytic agent is recommended in a consensus protocol using rFVIIa in elective orthopaedic surgery in patients with inhibitors.50 Reviews of adverse events related to the use of rFVIIa have not highlighted any association with antifibrinolytic agents.12,13,56,72 Caution using antifibrinolytic agents may be appropriate in situations associated with significant risks for arterial or venous thrombosis, as well as in pulmonary, intracranial or urinary tract haemorrhage. Combined or sequential use of APCCs is not recommended in the Australian and New Zealand data sheet. Published data have, however, demonstrated efficacy of sequential therapy using both rFVIIa and APCC in patients with refractory bleeds.73

Practical dosing

Practice points

• An automated intermittent bolus pump device may simplify the dosage schedule

• rFVIIa should not be mixed with infusion solutions

Failure to respond to treatment with rFVIIa may be due to a suboptimal dosing regimen. If response is inadequate, the dose and dosage frequency should be assessed. A high initial dose of rFVIIa, followed by down-titration, may optimise outcome.23 An automated intermittent bolus pump device can simplify the dosage
schedule by keeping to the recommended dosage interval (e.g. overnight; in busy hospitals with limited resources). In vitro data show that rFVIIa remains stable when reconstituted with an inappropriate solvent (sterile water for injection or saline) or at inappropriate volumes, but rFVIIa should not be mixed with infusion solutions.8

Conclusions

rFVIIa has been demonstrated to be safe and effective, and should be considered a first-line therapy for acute bleeds and surgical prophylaxis in patients with haemophilia A or B complicated by inhibitors. Haemophilia with inhibitors is a rare condition and management is complex. Published data on inhibitor management are limited, there are no reliable assays to monitor the effectiveness of therapy or to individualise dosing, and management is based largely on clinical response. This practical usage guide was therefore prepared by an expert group of haemophilia specialists from Australia and New Zealand to guide management. Practice points were developed for 13 key topics with agreement from all members of the expert group.

Important considerations are: early identification and assessment of bleeds as a medical emergency; immediate initiation of treatment at an adequate dose and dosing frequency; assessment by haemophilia specialist with continued close supervision and bleed monitoring; escalation or change of therapy in non-responders and consideration of prophylaxis to prevent recurrent bleeds. Concomitant medication with antifibrinolytics is usually appropriate. Access to home therapy is important in allowing patients to administer treatment early in bleed management.

These practice points provide guidance for clinicians on the usage of rFVIIa for haemophilia complicated by inhibitors.

Acknowledgement

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Nakar C, Cooper DL, DiMichele D.
Nutritional status of long-term patients in the acute care setting

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Abstract

The nutritional status of 926 patients (51.4% female) at an acute tertiary private hospital with a length of stay ≥14 days was assessed using Subjective Global Assessment. The prevalence of malnutrition was 42.5% (37.2% length of stay of 14–27 days, 51.6% ≥28 days). From logistic regression analysis, length of stay and age were independent predictors of malnutrition. It is important that the nutritional status of longer stay patients is monitored and appropriate nutrition support is commenced.

Malnutrition is recognised internationally as an issue in the hospital setting.1–3 The prevalence of malnutrition in hospitals across Australia varies between 12% and 42% depending on the timing and the nutrition assessment tool used.3 A recent cross-sectional study of 56 Australian and New Zealand hospitals (n = 1550) found that 30% of patients were malnourished using Subjective Global Assessment (SGA).4

Although there is evidence that poor nutritional status is associated with longer length of stay (LOS),2,4,5,7–15 the majority of studies uses individual nutrition parameters to assess patients’ nutritional status.5,6,15 As the reliability of these parameters has been questioned because of the number of non-nutrition-related factors that may affect the data, comprehensive nutrition assessment tools, such as SGA, are recommended.16 There is currently little published evidence on the prevalence of malnutrition in long-stay patients. Only one multisite Cuban study (n = 1905) demonstrated a significant increase in malnutrition from 36.8% on admission to 49.7% more than 30 days after admission using SGA.3 The aim of this study was to determine the prevalence of malnutrition in patients with increased LOS in a private tertiary hospital.

The study was conducted as part of routine practice at a 530-bed tertiary private hospital in Brisbane, Australia from March 2008 to May 2010. Adult patients were considered eligible for inclusion if their LOS was ≥14 days. Palliative care, rehabilitation, psychiatric and maternity patients were excluded from the study. Ethics approval was granted from the Multidisciplinary Ethics Committee of Uniting Care Health. The study population consisted of 926 patients, mean age (±standard deviation) 69 (13.9) years with 476 (51.4%) female.

LOS of ≥14 days was selected on the basis that it was at least twice the average LOS of the facility and LOS management practices at the hospital are focused on ≥14 and ≥28 days. One day each week, accredited practising dietitians assessed the nutritional status of patients using SGA. This validated tool determines nutritional status from a clinical history (weight change, food intake, nutrition impact symptoms present >2 weeks, changes in physical capacity) and a physical examination (subcutaneous fat loss, muscle wasting, ankle/sacral oedema and ascites).17 Each patient was classified into a global rating: well-nourished (SGA A), moderately or suspected of being malnourished (SGA B), or severely malnourished (SGA C). Following discharge, LOS, gender, date of birth

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and admitting specialty were recorded. If nutritional status was assessed more than once during admission, only the final assessment data were included.

Statistical analysis was performed using R for Windows (version 2.11.1, 2011, The R Foundation for Statistical Computing, Vienna, Austria). Logistic regression (LR) was used to determine if LOS group (14–27 vs ≥28 days) was a significant predictor of malnutrition (SGA B or C). Separate multivariable LR analyses were performed for each LOS group to evaluate the significance of gender, age group and specialty in predicting malnutrition. These analyses were repeated for malnourished patients only to examine which variables were associated with severe malnutrition.

To investigate further the effect of LOS, for all patients aged between 54 and 90 years with LOS 14–40 days, the probability of being malnourished was investigated using a model that included both age and LOS as continuous variables in addition to gender and specialty. A reduced model was also fitted that excluded gender and replaced the four-category specialty variable with an indicator of whether the patient was admitted to an oncology specialty. The superior model was identified on the basis of the significance of model coefficients and Akaike’s information criterion. For comparison between levels of categorical variables, referents were females, age group 61–80 and general medical specialty. Results include P-values for tests of significance of LR model coefficients and odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Overall significance of categorical predictors in LR models was assessed using Wald’s chi-square statistic. A separate Chi-squared test was used to assess independence between SGA rating and gender. Statistical significance was predetermined at the conventional level of P ≤ 0.05.

The prevalence of malnutrition was 42.5% (n = 394). Of patients with an LOS of 14–27 days, 37.2% (n = 217) were malnourished (32.6% moderately malnourished; 4.6% severely malnourished), and those with an LOS ≥28 days, 51.6% (n = 177) were malnourished (42.6% moderately malnourished; 9.0% severely malnourished). Compared with patients with LOS of 14–27 days (n = 583), patients with LOS of ≥28 days (n = 343) had significantly higher odds of being malnourished (OR = 1.8, 95% CI 1.4–2.4, P < 0.001). Although the odds of being severely malnourished was higher for those with LOS ≥28 days (OR = 1.5, 95% CI 0.9–2.6), this was not significant (P = 0.159).

The relationship between gender, age, admitting specialty, nutritional status and LOS are shown in Table 1. Gender was not associated with nutritional status; however, both age and admitting specialty were significant predictors of malnutrition for both LOS groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Malnourished</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
<th>Malnourished</th>
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<th>P-value</th>
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<td>Poor</td>
<td>0.5 (0.3–0.7)</td>
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<td>107 (56.8)</td>
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<td>107 (57.7)</td>
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<td>1.0‡</td>
<td>Medical</td>
<td>112 (31.3)</td>
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</tbody>
</table>

Table 1 Results of logistic regression analyses for all patients with 14 ≤ LOS < 28 and LOS ≥ 28 – gender, age, specialty and malnutrition

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Models were fitted to data from all patients aged between 54 and 89 years with LOS 14–40 days to study further the effect of LOS on the probability of being malnourished. Results from the model that included age and LOS as continuous variables in addition to gender and speciality indicated that gender was not a significant predictor of being malnourished ($\chi^2_{1(1)} = 0.77, P = 0.77$). Although speciality was significant ($\chi^2_{2(1)} = 34.1, P < 0.001$), only oncology patients exhibited different odds of being malnourished when compared with general medical patients (OR = 2.65, 95% CI 1.65–4.30). In light of this, we fitted a reduced model that excluded gender and included the oncology speciality (Table 2). The odds of being malnourished increased by 1.03 (95% CI 1.01–1.05) for an increase in age of 1 year, assuming that all other variables remain fixed. Similarly, the odds of being malnourished increased by 1.03 (95% CI 1.01–1.05) for an increase in LOS of 1 day, assuming that all other variables remain fixed. For patients with an LOS of 14–40 days and aged 54–89 years, oncology patients had significantly higher odds of being malnourished (OR = 2.92, 95% CI 2.02–4.23).

This observational study is the first conducted in Australia to determine the prevalence of malnutrition in long-stay hospital patients. For patients with LOS ≥14 days, the prevalence of malnutrition was 42.5%. Over half (51.6%) of the patients assessed with LOS ≥28 days were malnourished, an increase of approximately 15% from those patients hospitalised for 14–27 days (37.2%). These results are more than twice the prevalence of malnutrition reported at the same facility on admission 16.9% ($n = 408$) and in a recent point prevalence study ($n = 147$) 19.7%. They are also higher than the 30% prevalence of malnutrition reported in 56 Australian and New Zealand Hospitals. As the socioeconomic status of patients in the private sector may be higher than that in public facilities, the prevalence of malnutrition in public long-stay patients may be even higher.

The findings in this study are in agreement with a cross-sectional study of 12 Cuban hospitals where almost half (49.7%) of the patients with LOS >30 days were malnourished. The nutritional status of a patient has been suggested to decline the more days accumulated in hospital because of the patient’s condition, acuity and hospital practices in relation to mealtimes, unfamiliar food and lack of assistance. Further research tracking nutritional status of patients from admission is warranted to determine if nutritional status of patients declines during admission or whether it is the patients malnourished on admission that have extended LOS.

Our results strongly suggest that LOS and age are both independent predictors of malnutrition (Table 2). With every year accumulated in age and each day accumulated in LOS, the odds of being malnourished significantly increased. In addition, those patients admitted under the oncology specialty had significantly higher odds of being malnourished. Similar results were also found in a Queensland multicentre study where oncology patients were 2.3 times more likely to be malnourished when compared with general medical patients.

These findings highlight the need for nutrition screening to be implemented not only upon admission to hospital but throughout the duration of stay for detection of those patients who are either malnourished or at risk of malnutrition. This supports the new Australian Council on Healthcare Standards EQuIP5 criterion 1.5.7 that recommends malnutrition screening upon admission to hospital and rescreening every week during admission, as a method to reduce the prevalence of malnutrition attributed to by length of hospital stay.

There are several limitations of this pragmatic study. Purposive sampling was used as the study was performed as part of usual practice. Due to daily variation in clinician workloads, the number of patients with LOS ≥14 days that received a nutrition assessment was not predefined. Although this potentially limits the generalisability of the results, the large study sample, distribution of age, gender and speciality increase confidence in the

<table>
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<th>Variables</th>
<th>No. of subjects</th>
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<th>P-value</th>
<th>$\chi^2$(df)$^\dagger$</th>
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<td>189</td>
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<td>&lt;0.001</td>
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<td></td>
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</tbody>
</table>

$^\dagger$Wald Chi-squared statistic for overall term. $^\ddagger$Referent. CI, confidence interval; LOS, length of stay; OR, odds ratio; —, not applicable.
representativeness of the sample. Seven dietitians performed the nutrition assessments; however, all were experienced at performing SGA and participated in ongoing professional development activities on the application and completion of the SGA.

In conclusion, the prevalence of malnutrition increases with LOS, and both LOS and age are independent predictors of malnutrition in this private tertiary hospital. It is therefore important that the nutritional status of longer stay patients is monitored.

References


Conflict of interest: will it ever end?
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Key words
clinical trial disclosure, clinical trials, conflict of interest, ethics.

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Abstract
Despite the inclusion of investigator–industry pecuniary and non-pecuniary associations in published clinical trials, the benefit of such disclosures may be limited. Two recent pivotal phase III drug studies that raised conflict of interest issues are discussed. It is recommended that in the future, a firewall should be erected between industry and investigators.

Disclosure criteria for authors adopted by the International Committee of Medical Journal Editors have made relationships between industry, researchers and their respective institutions more transparent. However, according to a recent editorial in this Journal ‘it is possible that, far from increasing the critical scrutiny of readers, mandatory disclose of interests may actually undermine it, by inducing a false sense of security that issues relating to potential conflicts of interest have been effectively dealt with through the disclosure process alone’. While clinicians, government and the community should be able to rely on the integrity of a pivotal phase III study, not infrequently, serious questions are still raised about the veracity of clinical trial results, probably facilitated by the disclosure of relationships between industry and researchers.

The JUPITER study was a large multicentre clinical trial prematurely terminated by the data and safety monitoring board when it was observed that rosuvastatin significantly reduced the incidence of major cardiovascular events when used for primary prevention. While an accompanying editorial believed the reported results to be additional evidence for statin therapy in primary prevention, it did raise concerns regarding long-term safety given the short study duration. However, more serious concerns were subsequently raised, including an interactive poll that revealed broadly two points of view. One accepted the results, the other expressed concerns about the effect of the sponsor on the trial results. The veracity of these results was further questioned by a meta-analysis of 11 trials, including JUPITER, involving 65,229 participants which failed to find evidence of benefit following statin therapy in all-cause mortality in a high-risk primary prevention set-up. While it is possible that rosuvastatin might have additional cardiovascular benefits when compared with other statins, a critical reappraisal of the JUPITER study concluded that ‘the results of the trial do not support the use of statin treatment for primary prevention of cardiovascular diseases and raise troubling questions concerning the role of commercial sponsors’. An accompanying editorial concluded that ‘researchers must be free of incentives to find any particular desired answers’. These comments were in part related to the observation that the majority of authors had financial ties to the sponsor and that the principal investigator was a co-holder of the C-reactive protein test patent used in the study and licensed to the sponsor. In addition, the chairman of the independent safety monitoring board that prematurely terminated the study was involved in other industry-sponsored lipid-lowering trials. Questions were also raised regarding inconsistent cardiovascular end-points.

The PLATO study demonstrated that ticagrelor, a new oral antiplatelet drug, was superior to clopidogrel, the current benchmark treatment for acute coronary syndromes. In a subsequent ‘viewpoint’, Serebruany raised...
a number of concerns regarding the trial results and conclusions; in particular, the observation that the outcomes may have varied depending on who collected the data, a third-party clinical research organisation or the study sponsor. For example, death rates were numerically lower in the USA (3.2% vs 3.8%) with clopidogrel, although this represented only 9.7% of the study population. In contrast, patients from Poland and Hungary although this represented only 9.7% of the study population were lower in the USA (3.2% vs 3.8%) with clopidogrel, malignancies, particularly with the sponsor, the investigator pool would be significantly diminished. Despite many investigators believing that their association with multiple companies minimises bias, this is a concept that is flawed. Pharmaceutical advisory boards, travel and lecture fees remain problematic, and rigorous guidelines are urgently needed.

Because of the difficulty of knowing if a specific relationship could contaminate a clinical trial, the belief that it is essential to establish a firewall between the supporting corporations and the independent investigative group that designs the trial and manages and analyses the data is gaining momentum. The methods section of a recent study included the following. ‘Hoffman-La Roche funded the trial. The funding body had no role in the design or conduct of the study, in any aspect of data management or analysis, in the reporting of the study results, in the writing of the manuscript, or the decision to submit the manuscript for publication’. Such a relationship is not unique and should become the norm, and in the long term, all parties should benefit. Nevertheless, conflicts of interest will always exist, what is important is how they are managed.

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SPECT ventilation perfusion scanning with the addition of low-dose CT for the investigation of suspected pulmonary embolism

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Key words
SPECT V/Q, ventilation perfusion, computed tomography, diagnosis, pulmonary embolism.

Abstract
Single-photon emission computed tomography (SPECT) ventilation perfusion (V/Q) scanning with low-dose computed tomography (LDCT) is an emerging imaging technique for investigation of suspected pulmonary embolism (PE). We aimed to estimate diagnostic utility of the combined technique using results from all patients referred in 2009 compared with final diagnosis and 6-month follow-up status. PE was diagnosed in 28 of 106 patients (26%), including in 2 of 80 (2%) with negative SPECT V/Q and LDCT. The estimated negative predictive value of SPECT V/Q for PE was 97%. LDCT was abnormal in 43 (41%) patients, including 41 patients who had negative SPECT V/Q. In 29 (27%) patients, LDCT provided information on alternative pathologies that accounted for presenting symptoms, and the combined technique had a diagnostic yield of 52%.

Acute pulmonary embolism (PE) is common1,2 and frequently fatal if untreated.3 Diagnosis is challenging even when PE is suspected, with debate about the best approach for accuracy and efficiency. Single-photon emission computed tomography (SPECT) ventilation perfusion (V/Q) scanning is a modality that is increasingly used for the diagnosis of PE. The technique represents a transition from planar to cross-sectional imaging, with data acquired tomographically and analysed as a three-dimensional dataset. SPECT V/Q overcomes the superimposition of lung with normal perfusion, which can mask PE and studies demonstrate enhanced sensitivity, specificity and marked reduction in the nondiagnostic rate compared with planar V/Q.4,5 SPECT V/Q is now available at many public and private facilities throughout Australasia, although accuracy data on its performance are still emerging.6 The addition of low-dose computed tomography (LDCT) in the same sitting for anatomical correlation is an even newer technique now being used; however, the benefit of LDCT remains to be quantified.

We report the outcomes of SPECT V/Q scans done for suspected PE at a 600-bed tertiary institution in terms of sensitivity and specificity, and describe the incremental benefit of the addition of LDCT to the diagnostic yield.

We reviewed all SPECT V/Q with LDCT scans done on patients referred to the Department of Nuclear Medicine, Sir Charles Gairdner Hospital in 2009 for suspected PE. Demographic and clinical information were obtained from review of case notes. We recorded presenting symptoms, smoking status, comorbidities, vital signs (including initial room air oxygen saturation, SpO2), Wells score, and final clinical diagnosis given by the attending physician. Six-month follow-up status was ascertained either from case notes or by telephone contact. Serum creatinine levels were obtained from an online pathology results system.

SPECT V/Q and LDCT were reported by two experienced nuclear medicine physicians blinded to clinical data and classified by consensus as positive or negative for PE using predefined criteria (PE diagnosed in the presence of >50% perfusion mismatch in an anatomical segment or ≥2 regions of perfusion mismatch regardless of size). Abnormalities detected by LDCT were categorised into likely pathologies and correlated to SPECT V/Q findings to suggest alternative diagnoses in those negative for PE.

To estimate the sensitivity and specificity of SPECT V/Q, a composite reference standard for PE was used. The reference diagnosis was PE if the final physician diagnosis was PE and there were no alternative diagnoses at 6
months; and not PE if the final physician diagnosis was not PE and there was no occurrence of venous thromboembolism (VTE) at 6 months. The study was approved by the local human research ethics committee.

There were 122 scans performed in 2009, with 106 patients having clinical and follow-up data available (Table 1). Fifteen patients were referred from other institutions and were excluded from analysis as clinical data was unavailable.

In 122 scans, SPECT V/Q was classified as positive for PE in 28 (23%), negative in 93 (76%) and equivocal in 1 (1%). The patient with the equivocal result (excluded from analysis) received a diagnosis of gastritis, had no LDCT abnormalities and was stable at 6 months. In the 106 patients analysed, SPECT V/Q was classified as positive for PE in 26 (25%) and negative in 80 (75%). Four of the 80 patients with negative scans had CTPA due to ongoing high clinical suspicion for PE. In two, CTPA was negative for PE and were classified as SPECT V/Q true negatives. In two, CTPA was positive for PE and were classified as false negatives; the CTPA appearances in these two were thought to represent chronic PE. During 6 months follow-up, there were no other diagnoses of VTE in those with negative scans, and no alternative diagnoses made in those with positive scans. There were 12 deaths (11%) in the follow-up period – 6 from malignancy, 1 each from PE, acute coronary syndrome, sepsis, heart failure, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS). One death from PE and one from malignancy occurred in those with positive scans. There were 106 patients analysed, SPECT V/Q was classified as positive PE in 26 (25%) and negative in 80 (75%). Four of the 80 patients with negative scans had CTPA due to ongoing high clinical suspicion for PE. In two, CTPA was negative for PE and were classified as SPECT V/Q true negatives. In two, CTPA was positive for PE and were classified as false negatives; the CTPA appearances in these two were thought to represent chronic PE. During 6 months follow-up, there were no other diagnoses of VTE in those with negative scans, and no alternative diagnoses made in those with positive scans. There were 12 deaths (11%) in the follow-up period – 6 from malignancy, 1 each from PE, acute coronary syndrome, sepsis, heart failure, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS). One death from PE and one from malignancy occurred in those with positive scans.

LDCT demonstrated pulmonary abnormalities in 43 (41%) patients and was normal in 63 (59%). In the 26 patients with a positive SPECT V/Q, the LDCT was abnormal in two (8%) patients, both consistent with small pulmonary infarctions. In the 80 patients with a negative SPECT V/Q, 41 (51%) had LDCT abnormalities – 14 of atelectasis or consolidation, 11 of pulmonary oedema, 9 of emphysema, 3 of pleural effusions, 2 of incidental nodules, and 2 of elevated hemidiaphragm. In 29 (36%), LDCT abnormalities contributed to final clinical diagnoses – 10 of left ventricular dysfunction, 10 of pneumonia, 8 of infective exacerbation of COPD and 1 of ARDS. Along with the 26 patients with a positive scan for PE, this provided a total of 55 patients with diagnostic information from SPECT V/Q with LDCT, for an overall diagnostic yield of 52%.

Using the composite reference standard for PE, 28 (26%) patients were classified as positive, and 78 (74%) were classified as negative. Based on the reference standard, the estimated sensitivity, specificity and negative predictive value (95% CI) of SPECT V/Q for the diagnosis of PE was 93% (83–100%), 100% (93–100%) and 97% (93–100%), respectively. There were 26 true positive, 78 true negative, and 2 false negative results.

The prevalence of PE by traditional Wells criteria7 was 3% (1/30), 23% (13/56) and 50% (5/10) in the low, moderate and high probability groups, respectively. The prevalence of PE by modified Wells criteria4 was 11% (6/55) and 32% (13/41) in the PE unlikely and PE likely groups, respectively.

The results of this study demonstrate that our initial experience with SPECT V/Q for suspected PE was one of reasonably high accuracy, similar to other studies of
SPECT V/Q performance (Table 2). Also, we found that the addition of LDCT added useful information by identifying alternative causes for the presenting symptoms, and contributed to the overall diagnostic yield.

To date, SPECT V/Q has not been evaluated against an independent objective gold standard for the diagnosis of PE, and investigations on the accuracy of the SPECT V/Q have necessarily relied on composite reference standards that include the imaging study itself (Table 2). This study utilised a similar composite reference standard, with a longer follow-up period than many previous investigations. Studies on planar V/Q have shown that false positive results can occur with a variety of pathologies, including vasculitis, pulmonary fibrosis and neoplasia. With such reference standards, the true false positive rate is very low, and the results are appropriate matched or reverse mismatched defects on V/Q in those with pneumonia, and pulmonary oedema being low in this study is supported by the lack of alternative diagnoses during the 6-month follow-up. The false negative rate in this study is very low, and the results are supported by the 6-month follow-up status that did not reveal any subsequent diagnoses of PE or VTE. This is similar to findings in other larger studies, suggesting that SPECT V/Q has excellent negative predictive value. Nonetheless, caution should be taken when accepting these estimates given the lack of an independent reference standard and the inevitable confounding influence of SPECT V/Q results on the reference standard in use, particularly with regards to the false positive rate as the true specificity is almost certainly lower than 100%.

The benefit to diagnostic yield with the addition of LDCT has not been quantified. Gutte and colleagues investigated the accuracy of SPECT V/Q with LDCT for the detection of PE compared with CTPA, and found that the addition of LDCT increased the specificity of SPECT V/Q while maintaining its sensitivity. This was due to the ability of LDCT to visualise abnormalities such as atelectasis, emphysema and consolidation that may explain SPECT V/Q defects. Several patients were allocated a false positive diagnosis of PE with SPECT V/Q alone due to the presence of interlobar fissures and paraseptal emphysema that were detected on LDCT.

In this study, we demonstrate that the addition of LDCT increases the diagnostic yield of the test by providing alternative diagnoses, which correlated to the final clinical diagnosis provided for each case. Findings on LDCT were correlated to characteristic defects on SPECT V/Q to provide alternative diagnoses in 29 (27%) patients. These include consolidation on LDCT with appropriately matched or reverse mismatched defects on V/Q in those with pneumonia, and pulmonary oedema on LDCT with preferential perfusion redistribution to the upper zones in left ventricular dysfunction. In patients where emphysematous changes are shown, heterogeneous ventilation defects on V/Q is indicative of COPD. In these instances, LDCT enables detection of structural inflammatory changes such as opacity or infiltrates, that when correlated to matched or reverse mismatched V/Q abnormalities is highly suggestive of infective exacerbation of COPD. However, it is important to note that diagnoses are often made based on other clinical data (e.g. history, examination, echocardiography and spirometry), and these results primarily reflect the contribution of useful information from LDCT.

Wells criteria have been used extensively in determining the likelihood of PE. Encouragingly, the prevalence of PE by traditional Wells criteria in this study are very close to pooled data from previous reports, including PIOPED II.

SPECT V/Q has several advantages over CTPA that make it an attractive first-line investigation for suspected PE. This includes non-nephrotoxic radioisotopes, lower total radiation dose (institutional average 1.5mSv for SPECT V/Q with 150MBq technetium-labelled albumin, 0.9mSv for spiral LDCT at110kVp 20mA and 4.0–12.0 mSv for CTPA depending on software and equipment).
and considerably lower breast radiation dose. Only very low volumes of intravenous radioisotope are required during the perfusion phase, allowing utilisation of small bore intravenous cannulae (23–25 gauge) in patients with difficult venous access. SPECT V/Q, however, is not without limitations. In particular, after hours availability is limited in many institutions, and a 30 min acquisition time means that CTPA remains the preferred investigation in unstable patients.

A final point of note is that patients in this study do not represent consecutive patients with suspected PE, but are referred in consultation with nuclear medicine physicians and selected mainly based on factors that make SPECT V/Q preferable over CTPA. This represents a selection bias and care should be taken when applying these results to a more general population.

In conclusion, the initial experience with SPECT V/Q at our institution has been one of high sensitivity and good negative predictive value for PE. The addition of LDCT increases the diagnostic yield of the test by providing information on alternative pathologies that account for presenting symptoms. SPECT V/Q is a useful diagnostic test for suspected PE with significantly higher diagnostic yield compared with planar V/Q, making it a viable first-line alternative to CTPA. In the setting of renal impairment, radiocontrast allergy and in younger females, SPECT V/Q should be considered the investigation of choice.

References
21 Li DJ, Stewart I, Miles KA, Wraight EP. Scintigraphic appearances in patients...
Healthcare burden of in-hospital gout

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Key words
gout, length of stay, hospital, healthcare costs

Abstract
The disease burden of inpatient gout has not been reported. Using a discharge diagnosis database and individual case record review, 77 patients who developed acute gout complicating a hospital admission for another reason were identified between January 2001 and April 2010 at The Townsville Hospital. A control group of 28,301 cases with identical principal diagnoses were similarly ascertained, along with a subgroup of 231 cases matched for age, gender and ethnicity. Patients with an admission complicated by acute gout stayed 6 days longer in hospital than matched control patients (9 days vs 3 days, \(P = 0.0005\)) with the same principal diagnoses and demographics. Patients with an attack of gout were more likely to be older, male or indigenous. Early diagnosis and appropriate treatment may help to reduce the healthcare costs of this overlooked disease.

In Western countries, gout is the most common inflammatory arthritis. In the United Kingdom and United States, the prevalence of gout is 1–2.¹ The prevalence of gout is higher in men and increases with age, with a prevalence approaching 7% in men over the age of 65.² Other risk factors associated with gout include dietary excess, alcohol, diuretics, low-dose aspirin and renal disease.³ It is associated with significant burden on patient quality of life, the health system and the economy.⁴

Acute gout in hospitalised patients presents a distinct clinical problem. First, gout is particularly prevalent in hospitals because the disease processes that lead to hospitalisation, such as acute renal failure,⁵ and treatments administered in hospital, such as diuretics and surgical procedures, all can precipitate gout. Second, diagnosing gout in hospital may be problematic, as there may be a number of reasons for acute pain and a gout diagnosis may be overlooked. Third, contraindications to colchicine and non-steroidal anti-inflammatory drugs,⁶ such as heart failure, renal impairment and elevated gastrointestinal bleeding risk, are common in inpatients.

A major undersupply of acute hospital beds in Australia has focused efforts on reducing inpatient length of stays.⁷ Acute gout might be expected to prolong inpatient length of stay; however, the additional bed use resulting from inpatient gout is yet to be reported. To measure this, a retrospective case-control study was performed where cases and controls were matched for principal diagnosis (not gout), and with cases having a recorded episode of inpatient gout while controls did not. Demographical details were also collected.

The Townsville Hospital discharge diagnosis database was interrogated for patient admissions that were coded under the International Classification of Diseases (10th revision) with a secondary diagnosis of gout (M10) and a
principal diagnosis other than gout for acute admissions from January 2001 to April 2010. This group of patients was further categorised according to the principal diagnoses. Subgroups that contained fewer than three patients were excluded because the sample size was considered too small. The group of principal diagnoses included ‘complications of diabetes’, ‘hypotension’, ‘angina’, ‘myocardial infarction’, ‘atrial fibrillation’, ‘congestive heart failure’, ‘stroke’, ‘pneumonia’, ‘chronic obstructive pulmonary disease’, ‘intestinal obstruction’, ‘cholecystitis’, ‘cutaneous abscess’, ‘cellulitis’, ‘acute renal failure’, ‘urinary tract infection’ and ‘wound infection’. Five subgroups were excluded: ‘Staphylococcus aureus sepsis’, ‘acute myeloid leukaemia’, ‘pyogenic arthritis’, ‘person undergoing rehabilitation’ and ‘person awaiting admission to residential aged care service’. It was felt that in these patients, the principal diagnosis was likely to confound the diagnosis of gout as a secondary problem, or the discharge was likely to be delayed for non-medical reasons.

During the study period (January 2001 to April 2010), 336 admissions were coded with a secondary diagnosis of gout. Each admission was independently reviewed by a clinical coder who coded for gout if it was mentioned in the medical records. After excluding the principal diagnoses with less than three cases and those that did not fit with the study, 112 patients remained in the gout group. To overcome the inherent rate of misclassifications in a clinical database, each individual medical record, discharge summary (EDS; Queensland Health, Brisbane, Qld, Australia) and laboratory results (AUSLAB, PJA Solutions, Melbourne, Vic., Australia) were examined. Only the patients who suffered from an acute attack of gout during the admission were included. Gout was confirmed if patients either had sodium urate crystals on joint aspiration (20 patients) or if they were diagnosed with gout and managed as such by the treating team (37 patients). Thus, 35 cases were excluded from the gout group because gout was miscoded as a secondary diagnosis. Twenty-four were excluded because there was no mention of acute gout in the medical records, three because gout was actually the principal diagnosis, four were outpatient visits coded as admissions, and in four, the coded diagnosis was incorrect. The control group was formed from all acute admissions during the same time period with identical principal diagnoses to the gout cases. Patients’ age, gender, ethnicity and length of stay were collected for cases and controls. A demographically matched subset of the control group was formed by randomly selecting three cases from the control group matched exactly for age, gender and ethnicity for each case in the gout group. Using SPSS Statistics version 17.0 (IBM Corporation, Armonk, NY, USA), descriptive statistics (mean, median and standard deviation) were measured for age and length of stay, the Mann–Whitney U-test was used to assess differences in age and length of stay between cases and controls, and Pearson’s Chi-squared test was used to assess differences in gender and ethnicity between cases and controls.

The final gout group had 77 cases from 71 patients, and the control group had 28301 cases. The incidence of gouty arthritis in the study population was 0.27%. This is likely to be an underestimate of the true incidence because some genuine cases of gout are likely to have not been recorded in the medical records and therefore would not have been identifiable in the database. And second, the rigorous exclusion criteria applied that ensured all cases actually had gout may have inadvertently also excluded some real cases.

The demographics of the inpatient gout population in this study appear to mirror the community gout population. The median age of the gout group was 68 compared with 61 in the control group (P = 0.004), with 83% of the gout group being male, as opposed to 58% in the control group (P = 0.0005) (Table 1). Indigenous patients were overrepresented in the gout group with 16.2% Aboriginal and 5.41% Torres Strait Islander compared with 11.01% and 1.85%, respectively, in the control group (P = 0.0005). Patients with inpatient gout stayed a median of 7 days longer than cases matched for principal diagnosis and 6 days longer than cases additionally matched for demographics (gout median 9 days, control median 2 days, P = 0.0005, demographically matched control median 3 days, P = 0.0005), suggesting that gout confers a significant burden on patients and on the health system.

Study strengths include the rigorous inclusion and exclusion criteria for the gout group, ensuring that all subjects in the gout group were verified to have acute gout by examination of the medical records and lab results. Another methodological strength is the controlling of casemix and demographics as confounding variables by only performing the length-of-stay comparisons between cases and controls who had the same principal diagnoses, age, gender and ethnicity. Nevertheless, unmeasured variables may continue to confound the results, as patients in the gout group may have additional unrecorded comorbidities, as well as more severe and complicated presentations of their principal diagnosis. There may be a bias towards coding episodes of gout that are more severe and difficult to manage, which may also artificially prolong the length of stay. Another bias arises from the observation that a significant proportion of the control groups stay only 1 day in hospital, while patients were excluded from the gout group if they only stayed 1 day because gout was likely to be a presenting diagnosis.
Although the study was conceived subsequent to data collection (retrospective), the clinical data were systematically and prospectively collected. The study findings would be strengthened if reproduced elsewhere. There appears to be a significant patient and health system disease burden because of in-hospital gout, with patients staying 6–7 days longer in hospital because of the gout. Reducing this burden may be possible by addressing risk factors, and by early recognition and treatment of acute gout. Unnecessary cessation of allopurinol during hospital admission was a common precipitant of gout in an Australian study suggesting that an education strategy for non-rheumatologist clinicians might be effective.

Introduction of hospital-wide protocols for the management of acute gout and early referral to a rheumatology service may also help. In the community, there may be value in education of primary care physicians to optimise the usage of urate-lowering drugs. This study serves to highlight the importance of this neglected problem.

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References

Increased mortality risk in congestive heart failure patients with comorbid sleep apnoea: 10-year follow up

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Key words
heart failure, sleep apnoea, obstructive, sleep apnoea, central, mortality, survival analysis.

Abstract
We aimed to determine the mortality rates of a congestive heart failure (CHF) research cohort during a 10-year follow up and compare survival between those with CHF only (controls), CHF and central sleep apnoea, and CHF and obstructive sleep apnoea. There was a significant detriment of survival in patients with CHF/central sleep apnoea compared with both CHF/obstructive sleep apnoea patients (mean survival time difference 3.8 years, \( P = 0.005 \)) and controls (mean survival time difference 4.0 years, \( P = 0.01 \)).

Congestive heart failure (CHF) is a common serious medical illness,\(^1\)\(^-\)\(^3\) which is associated with a high risk of morbidity and mortality.\(^2\) Both central sleep apnoea (CSA) and obstructive sleep apnoea (OSA) are common among patients with heart failure.\(^4\)\(^-\)\(^6\) Research has shown that interventions to improve cardiac function can also improve indices of CSA and possibly OSA,\(^7\)\(^,\)\(^8\) suggesting that CHF can promote sleep apnoea. Conversely, the repetitive periods of breathing cessation characteristic of CSA and OSA may contribute to the onset of CHF through mechanisms such as myocardial hypoxaemia and sympathetic activation.\(^9\)\(^,\)\(^10\)

We have previously reported that 68% of patients with stable CHF have comorbid sleep apnoea, which is predominantly obstructive in nature (53% diagnosed with OSA; 15% diagnosed with CSA).\(^11\) These findings led to a second study in which 19 patients from our original CHF cohort with comorbid OSA were prescribed the first-line treatment for OSA, continuous positive airway pressure (CPAP).\(^12\) It was found that 6 months of CPAP treatment led to improvements in left ventricular ejection fraction, systolic blood pressure and daytime sleepiness but did not improve sympathetic activation, brain natriuretic peptide levels (a marker of cardiovascular disease), heart failure symptoms or exercise capacity compared with controls. Acceptance of CPAP treatment was relatively low with only 37% of patients using CPAP \( \geq 2 \) h/night after 6 months, which probably limited its effectiveness as those who used CPAP longer each night had a greater increase in left ventricular ejection fraction.

Only a few studies have been published that have analysed the effects of CPAP in CHF patients with comorbid OSA, and to our knowledge, none has followed patients for longer than 6 months.\(^12\)\(^-\)\(^15\) This study therefore aims to determine the living status of our original cohort of CHF patients (\( n = 53 \)),\(^11\) and compare mortality between those with CHF only (controls), CHF and CSA, CHF and treated OSA, and CHF and untreated OSA.

This study was granted ethical approval from the Central Region Ethics Committee (CEN/10/05/022) and, being an analysis of mortality, did not require informed consent.

Details of the original CHF research cohort (\( n = 53 \)) were retained by WellSleep. These were submitted to the Analytical Services Branch of the New Zealand Ministry of Health, who provided the status (alive/dead), and if death had occurred in 2008 or earlier, a cause of death. The primary outcome measure for each patient was the number of months between original consent and death, or if alive, the number of months between consent and the Ministry of Health database search (15 December 2010).

The cohort, shown in Figure 1, was identified as being controls (CHF only, Group A; \( n = 17 \)), CHF and untreated OSA (Group B; \( n = 21 \)), CHF and treated OSA (Group C; \( n = 7 \)), and CHF and CSA (Group D; \( n = 8 \)). Descriptive
The characteristics of the cohort are presented in Table 1. Kaplan–Meier survival analysis log-rank tests were conducted comparing controls and CSA patients (A vs D), controls and treated OSA (A vs C), controls and untreated OSA (A vs B), treated OSA and untreated OSA (B vs C), and OSA (both treated and untreated) and CSA (B/C vs D). To account for multiple comparisons, results were considered statistically significant when $P \leq 0.01$ (Bonferroni correction).

At the time of the Ministry of Health database search, 47.1% of the controls (Group A) were alive, 33.3% of the untreated OSA group (Group B) were alive, 42.9% of the treated OSA group (Group C) were alive, and 12.5% of the CSA group (Group D) were alive. Mean ± standard deviation (SD) survival time from initial consent was 85.6 ± 41.0 months in controls, 82.8 ± 41.5 months in untreated OSA patients, 83.4 ± 36.7 months in treated OSA patients and 37.1 ± 36.3 months in CSA patients. Of those who died in each group, mean ± SD survival time was 55.3 ± 33.5 months in controls, 61.9 ± 35.2 months in untreated OSA patients, 58.0 ± 25.4 months in treated OSA patients and 24.9 ± 11.4 months in CSA patients.

Of the nine controls who had died, cause of death was unavailable for two, as the Ministry of Health was only able to provide this information if death had occurred prior to 2008. Five controls had a cardiac-related cause of death and two non-cardiac (cholangitis and asthma). Of the 14 untreated OSA patients who had died, cause of death was unavailable for one, eight had a cardiac-related cause of death, and one died of complications relating to type 2 diabetes mellitus. Of the four treated OSA patients who had died, cause of death was unavailable for one, and the remaining three had cardiac-related causes of death. Finally, of the seven CSA patients who had died, cause of death was cardiac-related for six, and one died from a malignant neoplasm. Cardiac-related causes of death comprised acute myocardial infarction, cardiomyopathy of any kind, chronic ischaemic heart disease and atherosclerotic heart disease.

There were no significant differences in survival between controls and those with treated OSA ($\chi^2(1) = 0.07$, $P = 0.80$), controls and untreated OSA ($\chi^2(1) = 0.47$, $P = 0.49$), or treated OSA and untreated OSA ($\chi^2(1) = 0.102$, $P = 0.75$). However, there was a significant difference between survival distributions comparing CSA patients and OSA patients ($\chi^2(1) = 7.86$, $P = 0.005$), and comparing controls and CSA patients ($\chi^2(1) = 6.50$, $P = 0.01$). The survival analysis plot comparing controls and CSA patients is shown in Figure 2.

These 10-year follow-up data indicate no significant detriment in survival for patients with CHF and OSA –
either treated or untreated—compared with patients with CHF only. Further, there was no significant difference in survival comparing patients with CHF and OSA who were compliant and non-compliant with CPAP 6 months after beginning treatment. In addition to being statistically non-significant, the mean survival time of all these groups fell within a range of 6 months. However, patients with CHF and CSA had a significantly higher mortality

Table 1 Baseline descriptive characteristics of study cohort

<table>
<thead>
<tr>
<th></th>
<th>CHF only (n = 16)†</th>
<th>CHF/untreated OSA (n = 21)</th>
<th>CHF/treated OSA (n = 7)</th>
<th>CHF/CSA (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.1 ± 7.0</td>
<td>57.4 ± 11.3</td>
<td>61.6 ± 10.6</td>
<td>62.3 ± 10.2</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>62.5</td>
<td>80.9</td>
<td>71.4</td>
<td>100</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8 ± 4.0</td>
<td>28.8 ± 6.5</td>
<td>30.9 ± 5.5</td>
<td>25.1 ± 2.1</td>
</tr>
<tr>
<td>Epworth Sleepiness score (/24)</td>
<td>7.3 ± 3.6</td>
<td>7.5 ± 4.8</td>
<td>10.4 ± 4.6</td>
<td>9.4 ± 4.3</td>
</tr>
<tr>
<td>Total AHI (events/h)</td>
<td>4.2 ± 3.0</td>
<td>26.4 ± 15.2</td>
<td>31.7 ± 16.9</td>
<td>42.6 ± 24.8</td>
</tr>
<tr>
<td>Central index (events/h)</td>
<td>0.3 ± 0.4</td>
<td>1.0 ± 1.5</td>
<td>2.3 ± 4.9</td>
<td>33.6 ± 21.7</td>
</tr>
<tr>
<td>Obstructive index (events/h)</td>
<td>3.9 ± 2.9</td>
<td>24.4 ± 14.9</td>
<td>29.1 ± 17.0</td>
<td>7.3 ± 9.8</td>
</tr>
<tr>
<td>Mixed index (events/h)</td>
<td>0.0 ± 0.1</td>
<td>1.1 ± 3.0</td>
<td>0.3 ± 0.5</td>
<td>1.7 ± 1.5</td>
</tr>
<tr>
<td>Time asleep with SaO₂ &lt;90% (%)</td>
<td>0.3 ± 0.6</td>
<td>8.3 ± 13.9</td>
<td>11.9 ± 21.5</td>
<td>3.0 ± 3.7</td>
</tr>
<tr>
<td>PO₂</td>
<td>83.5 ± 11.4</td>
<td>74.7 ± 11.1</td>
<td>81.9 ± 6.5</td>
<td>79.3 ± 9.5</td>
</tr>
<tr>
<td>PCO₂</td>
<td>40.0 ± 3.4</td>
<td>39.2 ± 3.5</td>
<td>38.6 ± 3.9</td>
<td>38.2 ± 3.3</td>
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<tr>
<td>LVEF (%)</td>
<td>35.0 ± 8.0</td>
<td>35.9 ± 7.8</td>
<td>36.3 ± 4.5</td>
<td>24.0 ± 10.4</td>
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<tr>
<td>Sinus rhythm (%)</td>
<td>100</td>
<td>81</td>
<td>71.4</td>
<td>50</td>
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<tr>
<td>NYHA class III/IV (%)</td>
<td>17</td>
<td>33.3</td>
<td>14.3</td>
<td>25</td>
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<tr>
<td>FEV₁ (%)</td>
<td>85.3 ± 14.7</td>
<td>85.1 ± 16.8</td>
<td>76.4 ± 19.8</td>
<td>84.9 ± 17.6</td>
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<tr>
<td>FVC (%)</td>
<td>82.8 ± 11.7</td>
<td>83.3 ± 13.2</td>
<td>78.7 ± 19.8</td>
<td>80.1 ± 11.0</td>
</tr>
</tbody>
</table>

†Descriptive data missing for one subject. Data are presented as percentages or mean ± standard deviation. AHI, apnoea hypopnoea index; BMI, body mass index; CHF, congestive heart failure; CSA, central sleep apnoea; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OSA, obstructive sleep apnoea; PCO₂, carbon dioxide partial pressure; PO₂, oxygen partial pressure; SaO₂, arterial oxygen saturation.

Figure 2 Survival curves for the congestive heart failure (CHF)-only group (controls) and the CHF and central sleep apnoea (CSA) group (P = 0.01). This figure plots survival as a function of time beginning with consent, with each downward step representing a death of one or more patients. (——) CHF only (Group A), (——) CHF and CSA (Group D).
rate than patients with CHF alone (average survival time difference of 4.0 years) and patients with CHF and OSA (average survival time difference of 3.8 years). Cause of death was cardiac-related for the majority of patients who had died. The mean survival time of the patients who had died in the control group, untreated OSA group and treated OSA group (4.6, 5.2 and 4.8 years respectively), but not the CSA group (2.1 years), was higher than the average of 2.5 years reported in the Framingham Study. \(^1\)

Our data suggest that CHF with comorbid OSA, whether treated or untreated, does not appear to have a detrimental effect on survival over and above the effects of CHF alone. However, CHF with CSA does appear to have a detrimental effect on survival beyond the effects of CHF alone. A similar conclusion was reached in a study with a duration of 4.5 years;\(^16\) however, the effect of CSA on mortality in patients with CHF is a matter of some debate given that other studies conducted over similar time periods have not reported this difference.\(^17,18\) As has been discussed elsewhere,\(^19\) there are crucial differences in the methodology of such trials, resulting in the need for large, prospective multicentre trials to address this issue while controlling for a range of covariates.

The major limitation with these survival analyses is the reasonably small sample size, which we were unable to account statistically for potential confounders, most notably age, using logistic regression. Further, it is likely that relatively small numbers of patients remained on CPAP treatment long-term; therefore, we cannot rule out a potential survival benefit of CPAP. Despite this, the current study makes an important contribution to the literature given the absence of studies analysing long-term outcomes of any kind, including mortality, in CHF patients with comorbid OSA. We did not systematically address the treatment of CSA, so further research should be directed towards whether treatment with oxygen or adaptive support ventilation has a positive effect on short-term indices of CHF severity and long-term mortality. If this were the case, it would provide support for rigorous screening of CHF patients for the existence of CSA and the provision of adequate treatment for these patients.

**Acknowledgements**

We thank the staff of the Analytical Services Branch of the New Zealand Ministry of Health for conducting the mortality database search. We also acknowledge the contributions of the researchers involved in the original CHF studies, notably Dr Katherine Ferrier and Associate Professor Brendon Yee.

**References**


LETTERS TO THE EDITOR

Clinical-scientific notes

A fatal case of ‘magic mushroom’ ingestion in a heart transplant recipient

A 24-year-old heart transplant recipient presented to hospital following a cardiac arrest 2–3 h after ingesting an unknown quantity of magic mushrooms.

The patient received a heart transplant 10 years previously for end-stage rheumatic heart disease. Her post-transplant progress was uncomplicated. At her last clinic review before death (9 years post-transplant), she was well with no physical limitations.

Six months later, 2–3 h after consuming magic mushrooms, she collapsed. She received no bystander cardiopulmonary resuscitation and was cyanosed and pulseless on ambulance arrival. With resuscitation, she had intermittent return of spontaneous circulation interspersed with ventricular fibrillation/ventricular tachycardias/bradyarrhythmias. Resuscitation continued for 100 min before she was declared deceased.

Autopsy confirmed a healthy cardiac allograft (no allograft vasculopathy). Plasma toxicology revealed a psilocin level of 30 μg/L (consistent with magic mushroom toxicity) and a tetrahydrocannabinol level of 4 μg/L. No alcohol or other common drugs of abuse were detected. The cause of death was determined by court-appointed experts to be psilocin toxicity.

Many species of toxic mushrooms exist. This report focuses on mushrooms with hallucinogenic effects (Psilocybe genus). Psilocybin and psilocin are the two main compounds responsible for hallucinogenic effects and act as partial agonists at 5HT1A, 5HT2A, dopaminergic and adrenergic receptors.

Psilocybin is absorbed from the gastrointestinal tract. Psychological effects begin 10–30 min after ingestion (at a plasma concentration of 4–6 μg/L) and last for 2–6 h. The toxicity of psilocybin is low (LD50 = 280 mg/kg in rats), a 60-kg person would need to ingest up to 17 kg of fresh mushrooms to reach this dose.

Acute effects involve all organ systems – cardiovascular (tachycardia, hypertension), neurological (headache, confusion, euphoria, muscle weakness, hallucinations, panic attacks), respiratory (transient hypoxaemia), gastrointestinal, renal, ocular and haematological.

Only two deaths have been previously reported directly attributable to magic mushroom ingestion, one because of neurological sequelae (somnolence and convulsions) 6–8 h after ingestion of an unknown quantity of magic-mushrooms. Post-mortem toxicology revealed very high plasma psilocin concentration (4000 μg/L). Details of the second are scanty. Other deaths reported are as a result of accidents or self-harm following mushroom ingestion.

Reported toxicity is variable and includes cardiovascular toxicity (arrhythmia, acute coronary syndromes and catecholamine-associated cardiomyopathy), multi-organ failure and syndromes consistent with excessive catecholamine stimulation. Injury related to the psychological effects of mushroom intoxication is also described. No specific antidote is available, and treatment is supportive.

To our knowledge, this case is the first reported death from a cardiac arrest because of ingestion of psilocybe mushrooms. Control of heart rate is dependent on interplay between the sympathetic and parasympathetic nervous system. In the context of heart transplantation, cardiac adrenergic receptors remain intact after denervation and become supersensitive to exogenous catecholamines. Partial sympathetic reinnervation may occur...
postoperatively in transplanted hearts; however, para-
sympathetic control remains absent in the majority of
patients.

We postulate that in this case excessive sympathetic
stimulation of the transplanted heart as a result of
Psilocybe mushroom toxicity led to fatal ventricular
arrhythmias.

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posterior encephalopathy after ‘magic

Disseminated herpes simplex virus
infection following epidermal growth
factor tyrosine kinase inhibitor therapy
for non-small-cell lung carcinoma

A 77-year-old man with metastatic non-small-cell lung
carcinoma (NSCLC) presented with symptoms of dehy-
dration and haematuria in the setting of 3 weeks of
diarrhoea following commencement of a novel epidermal
growth factor receptor tyrosine kinase (EGFR TK)
inhibitor, afatinib. His NSCLC was initially managed with
gefitinib prior to disease progression warranted com-
 mencement of afatinib. The patient had not received any
myelosuppressive chemotherapy or corticosteroids. He
was Eastern Cooperative Oncology Group performance
status grade 0 prior to hospital admission.

On presentation, his neutrophil count was 6.99 ×
10^9/L (normal 2.0 to 7.5 × 10^9/L), his lymphocyte
count was 0.77 × 10^9/L (1.0 to 4.0 × 10^9/L), and his
creatinine was 141 μmol/L (60–130 μmol/L).
Urinalysis identified ≥1000 × 10^9/L isomorphic red blood cells
(normal <10). On day 2 of his admission, he developed
acute peritonitis secondary to colonic perforation. His-
topathology of excised bowel revealed multiple discrete
ulcers with perforations, but no viral cytopathic effects.
Postoperatively, he had abnormal liver function tests
with an alanine aminotransferase level of 98 IU/L
(0–50 IU/L).

On day 8, he developed haematemesis and underwent
a gastroscopy that revealed oesophagitis. Histopathology
showed reactive changes in oesophageal epithelium with
intranuclear viral inclusions, confirmed to be herpes
simplex virus (HSV) type 1 (HSV-1). HSV-1 was also
identified by polymerase chain reaction analysis of serum
(cycle threshold 33, lowest limit of detection 45). He was
 commenced on intravenous aciclovir (5 mg/kg three
times daily). Clinical examination did not reveal muco-
cutaneous HSV infection at other sites. The patient was
not sexually active and described infrequent episodes of
perioral HSV infection.

Immunological screening investigations were per-
formed; the patient was human immunodeficiency virus-
negative, had normal immunoglobulin levels, and had
depleted CD4 and CD8 counts of 0.17 × 10^9/L (normal
0.45 to 1.70 × 10^9/L) and 0.16 × 10^9/L (normal 0.20 to
1.15 × 10^9/L), respectively. He responded clinically to a
2-week course of treatment and secondary prophylaxis
with valaciclovir (500 mg daily) was then commenced.

Afatinib, a novel irreversible (BIBW 2992) EGFR and
human EGFR (HER) TK inhibitor has been developed as
first-line and salvage treatments for NSCLC. EGFR TK
inhibitors have predominantly dermatological and gas-
trointestinal adverse effects and low reported infection
rates. HSV-1 infection generally involves oropharynge-
al sites, but less frequent and more severe manifesta-
tions include disseminated disease with viraemia. The
oesophagus is often involved in disseminated HSV, and oesophagitis is more common in immunosuppressed patients.\(^5\) Our case demonstrated features consistent with disseminated HSV infection: biopsy-proven HSV oesophagitis, HSV-1 viraemia, extensive colonic mucosal ulceration, hepatitis and haematuria. Lymphocytopenia observed in association with afatinib may have contributed to risk for HSV infection as CD8 lymphocytes play a critical role in the control of HSV infection and latency.\(^6\)

To our knowledge, this is the first reported case of disseminated HSV infection in association with EGFR TK inhibitor therapy. In this instance, there was no known immunodeficiency or concurrent myelosuppressive treatment, strengthening a possible causal relationship that warrants heightened awareness and further study.

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References


A dangerous combination: Fabry disease and factor V Leiden

In 2011, Tchan and Sillence reported a 45-year-old man with stroke and the combination of Fabry disease (mutation (c.931delC)) and factor V Leiden.\(^1\) This combination has previously only been mentioned in two reports,\(^2,3\) although factor V Leiden mutation is quite common (0.5–5% carrier frequency in the American population\(^4\)), and one should expect the coexistence of factor V Leiden and Fabry disease in every large Fabry patient cohort. Moreover, Tchan and Sillence discuss some elementary important pathological pathways that are of major interest in Fabry disease.

We here report two first-degree relatives with factor V Leiden mutation and Fabry disease and highlight some of the discussion points mentioned by the interesting paper of Tchan and Sillence.

Three out of 175 patients (1.7%) in our Fabry Centre in Wuerzburg present the combination of Fabry disease and factor V Leiden mutation. One patient has already been reported by Möhrenschlager et al.\(^3\) The first two patients are relatives, namely father and daughter, not related to the already reported patient. The diagnosis of Fabry disease was known in the father since the age of 14 based on typical cornea vortices and angioma. The patient had multiple pulmonary embolism and deep vein thrombosis in the past. The clinical investigation programme of the main involved organs, the heart, kidney and central nervous system, revealed: (i) a severe cardiomyopathy with a septal wall thickness of 18 mm and fibrosis in the lateral basal wall, (ii) chronic kidney disease grades III-IV and a proteinuria, which improved after angiotensin-converting enzyme antagonist administration, and (iii) an ischaemic stroke in the territory of the right arteria cerebri media at the age of 54. The alphagalactosidase A activity was 0.03 nmol/minute/mg protein (normal >0.4 nmol/minute/mg protein) and the lyso-Gb3 84 ng/mL (normal ~0.4 ng/mL). Genetic analysis revealed the c.718–719 del AA fs 248X mutation. The same Fabry mutation was found in his daughter, who also carried the heterozygote factor V Leiden mutation. She was 23 when she first experienced transitory ischaemic attack and had an ischaemic stroke in the territory of the left arteria cerebri media at the age of 28. There was no evidence of heart or kidney involvement at latest follow up. Her alpha-galactosidase A activity was 0.19 nmol/minute/mg protein and the lyso-Gb3 5.4 ng/mL.

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Based on the results of our two patients and in addition to the detailed review of Tchan and Sillence, we want to highlight three topics.

First, similar to the patient reported by Tchan and Sillence, our two first-degree relatives experienced central stroke, although the overall prevalence of stroke in Fabry disease is only around 13%. This emphasises the already-mentioned hypothesis that because of the two genetic diseases, the risk for stroke is markedly increased (potentiating effect) in patients suffering from both factor V Leiden and Fabry disease.

Second, they stress the fact that the new biomarker lyso-Gb3 might play an important role in the pathogenesis of Fabry disease manifestations. However, they do not report the value of lyso-Gb3 in their patient, which would be of interest. Lyso-Gb3 is a spontaneous degradation product of the accumulating globotriaosylceramides. It is known as a verotoxin receptor since the 80s of the last century. The first to show that lyso-Gb3 is a hallmark for Fabry disease were Aerts et al. in 2008. They proved that lyso-Gb3 is increased in plasma of affected male Fabry patients and also in the plasma and tissues of Fabry mice. In addition, it was discussed that lyso-Gb3 plays a major role in the pathophysiology of Fabry disease. The lyso-Gb3 of our two patients is quite high when compared with other reports of Fabry patients with the same age. It can be speculated that there might be not only a ‘numerical’ addition of stroke-incidence, as explained earlier, but also a pathophysiological interaction of the two diseases. It is known that patients having very high lyso-Gb3 levels often present white matter lesions in early years of life. Lyso-Gb3 and other storage products in Fabry disease might be responsible for a prothrombotic status. This, together with the thrombotic capability of factor V Leiden, might lead to early stroke.

Third, we want to emphasise important aspects that always arise when diagnosing rare diseases. Although Fabry disease is rare and might give promising explanations for a specific clinical presentation, patients can suffer in addition from another rare genetic disease – like factor V Leiden mutation. If, in addition, symptoms of the one disease are mimicked also by the other disease, it is not always easy to make the correct and especially complete diagnosis. However, both the report by Tchan and Sillence, and our two first-degree relatives suggest that in all Fabry patients presenting with stroke or thromboembolism, a screening for the factor V Leiden mutation should be done. This is clinically important because in patients with both mutations, a more aggressive anticoagulation might be necessary.

References
Antibiotic treatment may exacerbate clozapine induced renal failure

We found the Bowen et al. report ‘Persistent febrile illness with multisystem organ failure associated with clozapine’1 very interesting. It adds to the growing number of cases establishing acute renal failure as a rare but serious side-effect of clozapine. We recently wrote a review article on this subject.2 We presented our own case and compared it with the seven other cases published at the time. In this most recent case, Bowen and colleagues elegantly and meticulously document something we had only postulated. Half of the eight patients with clozapine-induced renal failure (CIRF) presented in our article were placed on antibiotics shortly after a clozapine hypersensitivity response caused fever. This is not surprising. Infection was suspected, and antibiotics were prescribed. However, in at least two of these four cases – this includes our own patient – the renal failure became worse following antibiotic administration. We speculated that antibiotics could exacerbate CIRF and gave a mechanism that might explain it.

The Bowen et al. report bolsters our argument in several ways. It demonstrates an association between IV antibiotic use and a need for dialysis, which we are taking as an indicator of more severe renal disease. Three out of the nine total reported cases of CIRF underwent dialysis and, in two of these cases, IV antibiotics were given as an empirical treatment. The Bowen et al. case is one and Fraser–Jibani’s case3 is the other. In both instances, the administration of IV antibiotics preceded a further deterioration of renal function that led to dialysis. The first case of CIRF reported4 also required dialysis, but neither oral nor IV antibiotic treatment was mentioned. In the other six cases, which did not need dialysis, IV antibiotics were not given. When we checked for the association between IV antibiotics and dialysis, Fisher’s exact test yielded a two-tailed P-value of 0.0833. Given the small number of reported cases, that level of significance is highly suggestive.

Also noteworthy is the persistence of fever in the Bowen et al. case. In Figure 1 of their report, fever lasted for 21 days and abated 2 days after 19 days of continuous IV antibiotic treatment was discontinued. The figure also shows fever spikes immediately following the introduction of the antibiotics vancomycin and meropenem. The temporal association of fever severity and antibiotic use supports the hypothesis that antibiotic treatment can exacerbate CIRF and prolong the hypersensitivity response accompanying it.

Bowen et al. express concern about polypharmacy in psychiatric patients. While there may be an indication for polypharmacy with antipsychotics in some clozapine cases,5 it is important to consider the potential nephrotoxicity of all medications, including antibiotics.

In summary, we recommend caution when interpreting fever as a sign of infection in someone who has recently started clozapine. Fever can be a sign of a hypersensitivity reaction and not infection. Giving antibiotics could make the problem worse.

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Reducing polypharmacy Don Quixote style

Betteridge and colleagues from Christchurch Hospital have provided useful information on the increase in long-term medications in their acute medical unit. The slogan of geriatric medicine in the 1980s could have been taken from the sheep in George Orwell’s groundbreaking novel *Animal Farm* written in 1946, which chanted ‘four legs good, two legs baaaad’. In the case of geriatric medicine, the slogan was ‘no medicines good, ten medicines baaad’.

I believe that the number of potentially inappropriate medications (PIM) is far more important than the total number of medications. Fifty-five per cent of 272 351 elderly surgical patients used a PIM during their surgical stay. In contrast, 18% of 744 elderly Germans used a PIM at home.

The use of PIM has declined greatly in my patients from 1980 to 2012. Anticholinergics top the list of PIM in the elderly. In 1980, many of my patients took three anticholinergics: a tricyclic antidepressant in full dose (150 mg nocte), a gut antispasmodic such as hyoscine and a bladder antispasmodic such as oxybutinin. Some took four anticholinergics when they added orphenadrine for musculoskeletal pain. In 2012, very few of my patients use more than one anticholinergic in full dose; the most common class is bladder antispasmodics. In 1980, many patients took antihypertensives with a high rate of adverse effects, such as reserpine, hydralazine, alpha methyl dopa and guanethidine. In 2012, adverse effects from antihypertensives are uncommon, and it is easy to switch to a new class (e.g. dry cough from an angiotensin-converting enzyme (ACE) inhibitor leads to a switch to an angiotensin receptor blocker).

The worst real windmill is anticholinergics in full dose. A typical patient has four chronic conditions, such as diabetes, ischaemic heart disease, COPD, osteoporosis and hypertension. Consensus guidelines for these conditions suggest an average of three medications per illness, which leads to 12 long-term medications. In the past 12 months, I admitted 405 elderly to an acute care ward at Wyong Hospital. Major adverse drug events were uncommon and often due to short-term medications, such as *Clostridium difficile* diarrhea after antibiotics, accidental overdose of oxycodone, and partial serotoninergic syndrome after the first dose of duloxetine in a patient on fentanyl patch and amitriptyline 25 mg.

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Do shorter emergency department stays increase in-hospital mortality?

I have read with interest the paper by Mitra et al. This paper analyses data from three hospitals that do not have any target around emergency department (ED) length of stay (LOS). With some exclusions, it looks at the cohort of patients across the hospital subdivided into four groups: those who had a time to disposition plan (TDP) of less than and greater than 4 h and those who were in ED for less than or greater than 8 h, n = 10 107.

The data show that those patients with a TDP of less than 4 h, but a total ED LOS greater than 8 h, had a significantly higher mortality than those who had a TDP...
greater than 4 h or those who had a TDP less than 4 h but an ED LOS less than 8 h (fig. 1 in the paper).

This article is a correlational study – and correlation is not the same as causality. In particular, the link between dwell time and outcome may be linked in either direction:

- Staff take less time to determine that a more seriously ill patient needs admission and more seriously ill patients have a higher mortality (state of illness causes both dwell time and mortality).
- Staff who reach a decision quickly make poor decisions, which lead to increased mortality.

The paper assumes the second but presents no data to support this conclusion.

The paper confuses LOS and TDP. TDP is defined as the time between arrival in ED and referral to an inpatient service or request for a bed, whichever is shortest. There is an implied conclusion in the paper that TDP is equivalent to time in ED and that the 4-h target is related to TDP (it does not – it relates to LOS, i.e. total time in ED).

In fact, the most at-risk patients are those where a decision to admit is reached quickly and the patient is handed over to the inpatient service (short TDP), but the patient then remains in ED for at least another 4 h. This is the group with 9.5% mortality, those patients where a decision is reached quickly, but access to inpatient services or beds is blocked for any reason. Where that block does not occur, mortality is 6.5%. For this reason, the data in the paper actually argue for a 4-h target not against one, as the authors suggest.

At the time of the study, none of the three hospitals involved was working to a 4-h target. This is noted in the paper. For this reason, one would assume that there was no pressure for quick decision making (certainly, the fact that only 33% of the patients in the sample were discharged from ED within 8 h would support that view). This would suggest (although there are no data in the paper on this issue) again that the main reason for TDP <4 h is clinical state rather than pressure to meet a target.

Finally, in the abstract, the authors state:
A perceived risk of time-limited emergency department (ED) assessment of patients is inadequate workup leading to inappropriate disposition.

And in their conclusions:
Effective solutions to access block, continuing surveillance and rigorous analysis of patients outcomes are required prior to adopting any change, which restricts history taking, a thorough examination, comprehensive investigation and acute management in the ED.

There is no evidence in the paper other than time to disposition that would suggest any of these factors were present in the three hospitals in this study. There is no evidence that history taking, examination or investigations were rushed; there is no evidence that patients needing acute management did not receive it; and there is no evidence presented that work-up in these patients was inadequate or led to inappropriate disposition.

In their discussion, the authors do identify the real issue presented by this data:
We have shown that a TDP of <4 h was associated with significantly shorter ED LOS compared with a longer TDP. However, when affected by an ED LOS ≥ 8 h, the shorter TDP was associated with a significantly higher mortality, even when adjusted for age, gender and triage category. Where ED LOS was shorter, this association was no longer significant.

Long LOS, especially in those patients where it is possible to identify quickly the need for referral to inpatient specialities and admission, leads to higher mortality.

Letters to the Editor

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Reference

Reply
We thank Cumming1 for his interest in patient flow and comments. We agree with his view that a long length of stay (LOS) in the emergency department (ED) is associated with higher mortality, and this association is amplified in patients suffering access block and a short time to disposition plan (TDP). The association of ED LOS with mortality has now been repeatedly shown, albeit from observational and retrospective analyses only, and it
should therefore be clear that avoidance of prolonged ED LOS should be the target of health policies.

However, Cumming makes some comments regarding the manuscript that we do not understand. TDP and LOS are clearly defined in our paper, and we remain unclear regarding any source of confusion regarding these definitions. The alternative explanation of the findings of this study – that more seriously ill patients have a shorter TDP – was also discussed. To reiterate, excluding patients requiring intensive care, cardiac monitoring and surgery, controlled for some of this bias, suggesting that the immediate mortality risk, would not have been obvious to the clinician on admission. Furthermore, the retrospective nature of this analysis resulting in concluding an association, rather than causation, was also discussed, and we were surprised that having made this point again, the author of this letter went on to state a causative conclusion in his final sentence.

The view that our manuscript argues ‘for or against a 4-hour target’ is also flawed – we were merely suggesting caution and greater vigilance. There is no doubt that performance targets have forced clinicians to make rapid disposition plans when not clinically appropriate. The design of current targets exposes our patients to the possible collateral damage of incomplete assessment in the ED while promoting a higher admission rate, longer hospital LOS, potentially further choking an already stressed system, together with massive financial burdens.

We understand the value of time targets in patient flow processes, but we would like to see targets more specific to the processes contributing to prolonged ED LOS and overcrowding. There needs to be acknowledged that the major cause of ED overcrowding is access block rather than clinical processes in the ED. Emphasis on a single time target, such as ‘4 hours’, will inevitably lead to distortions in clinical care, and it is important that we develop more sophisticated methods for monitoring performance. Health policies promoting safe medical practice should focus time targets at the root cause of the problem – on access to hospital beds, at the conclusion of clinical processes – not on the clinical processes themselves.

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Guidelines on guidelines – the impact of the Web

Morris et al.’s recent article, a remarkably long and comprehensive critique of The Royal Australasian College of Physician’s policy statement regarding circumcision of male infants, raises important more general issues concerning guidelines issued by respected organisations.

Such guidelines are more frequently promulgated than previously and, because of the advent of the World Wide Web, are more accessible being readily available not only to professionals but also to the general public. Notwithstanding this, the authorship and even sometimes the process of their development are often not stated. In addition, such guidelines are not always referred for anonymous peer review. In some instances, such a review would be hard to acquire as most of the opinion leaders within the country (or group of countries) in the relevant field of expertise may have been involved in the writing of the guidelines. To request an international
review is an option, but such a reviewer may not be familiar with the unique economic and social milieu in which medical practitioners work in the original country. Possibly most importantly of all, there is no or limited opportunity for comments to be made on the website of the organisation, which is sponsoring them. There is also the reciprocal inability of the authors of the guidelines to make replies to commentary made in another publication – this was particularly pertinent with respect to Morris et al.’s article, which left the reader hankering for a reply to the criticisms. I therefore have the following suggestions:

1 Guidelines should be developed in as inclusive a manner as possible and according to recognised methodology. There are several published approaches.2,3

2 Anonymous peer review of the guidelines should be encouraged notwithstanding the limitations outlined above.

3 Guidelines should be labelled as ‘provisional’ at least for the first few months after being posted on the sponsoring website, and there should be opportunity for interested observers to comment (anonymously if desired) on such provisional guidelines. In some instances, such commentaries should remain on the website until the guidelines themselves are no longer extant.

4 The members of the organisation should all be emailed the provisional and final guidelines.

5 The authors of the guidelines and the nature of each author’s contribution to the guidelines should be stated.

6 Guidelines should be regularly updated, and the date of the promulgation of each version should be stated.

7 If consensus eludes the working party, appointed to formulate the guidelines, all members should be emailed advising of this eventuality.

8 If guidelines are developed in the face of significant differences of opinion within the working party, key points of disagreement should be enunciated in a supplementary document.

Some issues in medicine incite passions at a community as well as at a clinical level. As a profession, we must cater for this in a way that is as sensitive and open as possible.

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Correcting Morris et al. with respect to anaesthesia for neonatal circumcision

In defence of The Royal Australasian College of Physicians (RACP), and having recently published a comprehensive review of anaesthesia for neonatal circumcision,1 Morris et al.2 make three claims to which I would like to respond.

1 That circumcision is best performed early in infancy using local rather than general anaesthesia – In support of this, the authors cite a single, 16-year-old, non-randomised, non-controlled, non-blinded, self-reported, descriptive study promoting the use of EMLA cream for mass neonatal circumcision in a commercial circumcision clinic.3 They failed to cite the five randomised trials and one systematic review that have since shown that EMLA cream is inferior to injectable local anaesthesia and provides insufficient anaesthesia for neonatal circumcision.4–9 They failed also to acknowledge the significant failure rates of even injected local anaesthesia for neonatal circumcision1 and the risk of distress because of restraint, needle insertion and infiltration.

2 That the RACP has not provided supporting evidence for its claim that neonatal pain has long-term consequences – This statement incorrectly implies that such evidence does not exist. All pain can have long-term consequences, and the immature neonatal nervous system is especially vulnerable. Taddio et al.,5 for example, demonstrated more than 15 years ago that neonates who had been circumcised without anaesthesia exhibited heightened distress in response to the pain of subsequent routine immunisations even 6 months later.

3 The members of the organisation should all be emailed the provisional and final guidelines.

4 The authors of the guidelines and the nature of each author’s contribution to the guidelines should be stated.

5 Guidelines should be regularly updated, and the date of the promulgation of each version should be stated.

6 If consensus eludes the working party, appointed to formulate the guidelines, all members should be emailed advising of this eventuality.

7 If guidelines are developed in the face of significant differences of opinion within the working party, key points of disagreement should be enunciated in a supplementary document.

Some issues in medicine incite passions at a community as well as at a clinical level. As a profession, we must cater for this in a way that is as sensitive and open as possible.

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Letters to The Editor
3 That neonates exhibit lower pain scores than older infants and that the pain can be negligible with local anaesthesia – Assessment of pain in neonates and young children is notoriously difficult precisely because their physical responses are muted, non-specific and unreliable. Lack of response to painful stimuli is well documented in neonates and infants, and must not be mistaken for an absence of pain.10

Our review confirmed that neonatal circumcision is a formal surgical procedure producing real tissue damage and significant intraoperative and postoperative pain.1 The RACP is correct in stating that anaesthesia is required for neonatal circumcision and is now recommending injectable local anaesthesia for younger boys and general anaesthesia for older ones.11 Given the elective nature of the procedure and the risk of failure with local anaesthesia, our review concluded, however, that deferment until after the age of 6 months, when all could be done under general anaesthesia, was the safest option. This is now the policy of the majority of Australian State Health Departments.3

References


Reply

We agree with Paix1 that appropriate anaesthesia be used for circumcision.1,3 But Paix advocates either the delay of infant male circumcision to ≥ 6 months and use of general anaesthesia (GA) or having GA available to rescue failed local anaesthetic,4 an approach some feel is suboptimal and inconvenient.3 GA adds to costs and risks, which may include risks to higher cognitive functions.6 The recommendation that ‘6’ months is optimal for elective anaesthesia, although accepted, is not evidenced based. The GA approach favoured by Paix includes fasting (6 h for solids, milk and formula), insertion of an intravenous catheter prior to induction of anaesthesia (requiring restraint and involving pain) and emergence delirium. Thus, GA is not free of distress.

An evidence-based assessment ‘may tip the pendulum back towards the other analgesia/anaesthesia options’.3 Even The RACP is balanced with respect to this; in its brochure, the ‘Royal Australasian College of Physicians (RACP) recommends the use of an injected local anaesthetic for very young boys’, although recommends GA at 6 months for older boys.7

In the first author’s experience of ≥ 5000 circumcisions using ultrasound-guided dorsal penile nerve block,8 this block is superior to no ultrasound and is superior to 5000 circumcisions with eutectic mixture of local anaesthetics 2.5% lidocaine and 2.5% prilocaine (EMLA) cream

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applied for 60–80 min, as used by Taddio et al. The procedure and injection each take 2 min, so total restraint time is ≤4 min. Adjuncts, such as paracetamol and sucrose, are used to minimise the discomfort of the injection. Most parents find their babies do not require paracetamol after 18–24 h. A ‘raw’ area on the glans takes 7–10 days to heal; the use of petroleum jelly and disposable nappies makes the healing period tolerable for babies and parents. Separation of glanular adhesions is required in most boys, sometimes up to 6 years of age, so this potential source of post-procedural discomfort is present even in older boys having the procedure under GA, contrary to Paix’s assertion.

Thus, what Paix says is inconsistent with the first author’s practice and observations, a view also expressed by the anaesthetists he uses. Circumcision in the neonatal period under local anaesthesia is safe and effective, and has no long-term adverse cognitive or other consequences. Many parents may agree with the view that local anaesthesia is preferable to circumcision under GA.

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Evidence-based policy: circumcision of infant males

Your recently published article on the current Royal Australasian College of Physicians’ (RACP) policy statement ‘Circumcision of infant males’ misrepresents the policy and the process of its development. In its introductory section, the statement by Morris et al. misquotes the RACP policy by omitting ‘routine’ from the statement ‘the frequency of diseases modifiable by circumcision, the level of protection offered by circumcision and the complication rates of circumcision do not warrant routine infant circumcision in Australia and New Zealand’.

Circumcision of infant males was recently reviewed to incorporate current evidence. The working group, assembled after calls for expressions of interest across the RACP, had the specific expertise of paediatricians, surgeons, a public health physician, an epidemiologist, paediatric ethicists, health policy advisors, epidemiologists of paediatric renal disease and a rabbinical council advisor. Rigorous methods were used to ensure that the research base was tested for its quality and relevance to healthy infant boys in Australia and New Zealand. The working group used the Scottish Intercollegiate Guidelines Network system of evidence evaluation, designating the power of the evidence in reviewed articles. The policy development process involved wide consultation with professionals, community groups and parent representatives.

The working group weighed the evidence, and with the best interests of the child in Australia and New

References
Zealand in mind, and arrived at a different conclusion to Morris et al. The working group concluded that there is insufficient evidence to recommend routine circumcision for healthy male infants in Australia and New Zealand. The policy acknowledges the appropriateness of well-informed parents undertaking this decision on behalf of their sons and also outlines the conditions under which circumcision should be undertaken.

The statement acknowledges that recommendations may be different in other social and health environments. It was noted that there is evidence in support of adult (not infant) circumcision in African countries with high prevalence of heterosexually transmitted HIV and sexually transmitted infections. Changing circumstances and changing evidence will require regular review of this and all health policies.

The most recent iterations of the American Academy of Pediatrics (AAP) position statement on infant circumcision draws similar conclusions to the RACP evidence-based statement. The AAP statement emphasises both the benefits and risks of circumcision, concludes that the benefits outweigh the risks and recommends that circumcision be available to US parents, but not that it be routinely performed. The Royal Dutch Medical Association takes a much stronger position against circumcision of healthy infant males, stating that newborn circumcision is a violation of children’s rights to autonomy and physical integrity. We are not aware of any organisations of child health professionals currently advocating routine newborn circumcision.

The RACP Circumcision of Infant Males policy, published in 2010, is evidence based and balanced, utilising both international and local research to come to a conclusion which in keeping with our societal obligations, supports the best interests of children, plus respects parents and guides clinicians.

References

Reply

We welcome the letter by Forbes responding to our critique of the 2010 Royal Australasian College of Physicians’ (RACP) policy on infant male circumcision. We note that significantly, Forbes was unwilling or unable to respond to any of our detailed and substantive criticisms. Therefore, our conclusion stands, namely that the RACP’s policy ‘ignores, downplays, obfuscates or misrepresents the considerable evidence attesting to the strong protection circumcision affords’ against a raft of medical conditions over the lifetime. We contend that if the RACP’s policy statement is not a fair and balanced representation of the current literature, then it should not be used to guide policy. Rather than presenting any new evidence-based material, his letter simply restates extracts from the RACP policy statement and persists in describing the 2010 policy as ‘evidence-based’. Forbes does not defend the decision not to use a literature-based risk-benefit analysis. The policy statement concluded that the currently available evidence does ‘not warrant routine infant circumcision in Australia and New Zealand’. We apologise for omitting the word ‘routine’ in quoting this text in our introduction, but note that we included the word ‘routine’ in the same quote appearing in our abstract. We recommend that circumcision be offered routinely to parents for an infant son.

Parents should be provided with accurate and up-to-date information about infant male circumcision. Those who then choose this option should be strongly supported and the intervention should be facilitated, just as applies to childhood vaccination.

Forbes refers to outdated policy statements not based on evidence, these being by medical bodies in other countries, but ignores our recently published, evidence-based affirmative policy statement that included a risk-benefit analysis. Subsequent to the submission of Forbes’ letter, the American Academy of Pediatrics released its new policy statement that like ours found the health benefits of circumcision outweigh the risks. Both
of these policies advocate measures to improve education and facilitate access.

We are pleased to learn from Forbes that the RACP committee was diverse and consulted widely. We note, however, that Forbes makes no mention of the extent of agreement reached.

We agree with Forbes regarding ‘the appropriateness of well-informed parents undertaking this decision on behalf of their sons’. The evidence supports performing circumcision during the neonatal period with local anaesthesia.2–5

We support the RACP undertaking an extensive, comprehensive, balanced review of the scientific literature and conducting a risk-benefit analysis. Australian parents deserve nothing less.

References

‘Circumcision of infant males’ must warn doctors of possible criminal assault charges

Morris et al., in their discussion of The Royal Australasian College of Physicians’ (RACP) male circumcision policy statement, overlook the question of whether it is lawful to perform non-therapeutic circumcision on minor boys.1 This question must be resolved prior to any discussion of the alleged health advantages or disadvantages of male circumcision.

The Queensland Law Reform Commission (QLRC) has considered this matter.2 In Marion’s case, the High Court of Australia ruled that parents cannot grant surrogate consent for the non-therapeutic sterilisation of a minor girl.3 The QLRC concluded:

The common law operating in Queensland appears to be that if the young person is unable . . . to give effective consent to a proposed procedure and if the nature of the proposed treatment is invasive, irreversible . . . surgery and for non-therapeutic purposes, then court approval is required before such treatment can proceed.3

Clearly, the lawfulness of non-therapeutic circumcision requires that valid consent is first obtained.2,4 A child cannot provide fully informed consent by reason of his immaturity and legal incapacity.2,4 Parental powers are derived from the parent’s duty to the child.3 The parental surrogate is limited by the common law to granting consent for what the child actually needs8 and is in the best interests of the child.4 In the absence of medical necessity, no child needs a circumcision, so a surrogate cannot grant valid consent,2–4 thereby making non-therapeutic circumcision of a child a criminal assault.4

Although no Australian court has yet ruled on this matter, a regional appellate court in Cologne, Germany has done so.7 In this case, the court held:
• That the medical doctor carried out the non-therapeutic circumcision for religious reasons at the request of the parents
• That circumcision violated the physical bodily integrity of the child
• That the child’s body was permanently and irreparably changed by the circumcision
• That the child could not consent by reason of his minority
Although the parents consented to the circumcision, surrogate consent was invalid because circumcision was not in the best interest of the child (parents must act only in the best interest of the child).

That circumcision for other than medical necessity must be deferred until the child can make his own fully informed decision and grant personal consent.

That the requirements for criminal assault had been satisfied.3

A court in Australia might easily reach a similar decision based on either domestic or international human rights law. There are no impediments to prevent such a decision and sufficient precedent, including Marion’s case,3 to believe that an Australian court would find non-therapeutic circumcision of children to be a criminal assault. Based on stare decisis, the Cologne precedent increases the probability that an Australian court would reach such a decision.

In the absence of a definitive ruling from an Australian court, the RACP should revise its circumcision policy statement, warning medical doctors to avoid possible civil and criminal liability by deferring non-therapeutic circumcision of children until they can personally grant fully informed consent.

References

Legal arguments opposing infant male circumcision are flawed

Now that prophylactic infant circumcision is supported by evidence-based policies in the USA1 and Australia,2 opponents have retreated to subjective legal arguments.3 Advising that ‘non-therapeutic’ [sic!] circumcision be delayed until the child gives consent is unwarranted.

Marion’s case considered the issue of parental consent in the context of a non-therapeutic sterilisation.4 The Queensland Law Reform Commission (QLRC) paper held that Court authorisation is required for non-therapeutic procedures if invasive, irreversible and ‘major’ surgery. Hill et al. conveniently omit the word ‘major’. ‘Invasive’ means ‘requiring insertion of an instrument or device into the body through the skin or a body orifice for diagnosis or treatment’.5 Perhaps removing the prepuce might not be considered entering the body. Circumcision is arguably irreversible, although a tiny minority of circumcised men have been known to participate in the eccentric practice of stretching their residual foreskin or shaft skin to ‘reclaim’ the lost prepuce. Circumcision is not, however, a major surgery. Accordingly, that test would not take circumcision outside the ordinary scope of parental consent. Although not legally binding, it is noteworthy that Judge Sir William Patrick Deane made the observation in Marion’s case that circumcision ‘for perceived hygienic – or even religious – reasons’ ‘plainly lies within the authority of parents of an incapable child to authorise surgery on the basis of medical advice’.

Although the 1992 QLRC paper took the view that circumcision met the test and thus parental consent could be invalid, it opined that while circumcision (in 1992) was not encouraged for medical reasons, there is an
argument that it should not be made unlawful because it may be in the child’s interest to be circumcised for cultural or religious reasons, but for other reasons, it ‘may be less clear’. Today, medical policy holds that it is a decision for parents and has benefits. Applying the same reasoning today would thus make prophylactic circumcision acceptable. Nevertheless, while allowing for civil liability, the QLRC opined that it is unlikely that a medical practitioner acting in good faith with due care would be criminally prosecuted.

The German Government says that it will legislate against the Cologne court’s highly criticised ruling. Thus, what Hill et al. argue is inconsistent with the opinion of a High Court judge and the better view of a test in Marion’s case. Circumcision in the neonatal period with informed parental consent, just as childhood vaccination, is permissible by law, and there is no need for those unqualified to practise law to give contrary advice.

Male circumcision

The topic of infant male circumcision is one that seems to arouse strong emotions. Further to Morris et al.’s recent criticism of The Royal Australasian College of Physicians’ policy document, I wonder if male authors of papers on this subject should declare their own circumcision state as a potential conflict of interest that may be influencing their views.

The giant waves of Osborn in brain death

Omar et al. describe ‘a severely cold patient in deep coma and absent brainstem reflexes denoting brainstem death’. I would like to suggest that at 26.9°C, the absence of any or all responses does not necessarily imply brain death. Similarly, with Glasgow coma score 3/15, the patient would presumably be intubated and ventilated, perhaps with paralysing agents for the procedure or specifically to stop shivering – hence, the absence of shivering may not mean much either in this setting. It is not always
recorded in hypothermia electrocardiograms anyway. The only electrocardiographic inference about brain death is the relatively insecure observation that the rate is faster than expected. I would have liked to hear that the patient was warm and dead – a time-honoured principle in critical care.

Reference

Reply
I thank Nikolić1 for his interest and thoughtful comments regarding the utility of the Osborn wave as a clue to raise suspicion for brain death in head trauma victims. Unlike developed countries where withdrawal of care is the standard management for brain-dead patients, the absence of similar rules and regulations in developing countries prohibits life termination, and mandates continued ventilatory support until circulatory collapse ensues. This process can last for hours to days and hence increased our exposure to the haemodynamic and electrocardiographic consequences in these patients. In our practice at a level-III trauma centre with a high-admission rate for motor vehicle accidents, we were vigorously exposed to traumatic brain injuries and brain death.

Hypothermia depresses central nervous system function2 and can mimic brain death. Adequate re-warming is mandatory prior to any neurological examination and making the diagnosis of brain death. However, the diagnosis in our trauma victims was made early prior to the onset of hypothermia. In this instance, hypothermia was a consequence of brain death rather than a cause for the patient’s unconsciousness. In head trauma, with no other reason for developing low temperature, the development of severe hypothermia is usually a sign of impaired thermoregulatory ability due to hypothalamic dysfunction. In brain death, hypothermia is usually progressive and irreversible. Our reported cases of brain death-induced hypothermia3,4 were not on any sedation and characteristically had Osborn waves without shivering artefacts in the surface electrocardiogram (ECG). Inability to mount a shivering response in hypothermia was associated with a worse outcome in previous studies.5

Drory et al. studied the electrocardiographic and haemodynamic changes in 28 patients with brain death.6 A common ECG finding was the appearance of the Osborn wave enveloping the terminal part of QRS complex which was evident in 24 out of the 28 cases.6 In most cases, the temperature in the initial stage of brain death was around 35°C, while in the terminal stage was 26°C–32°C.6 We can hypothesise that, in head trauma victims, specifically those who are not on any sedation and with no other evident cause for hypothermia, the development of hypothermic Osborn waves without shivering artefacts in the ECG should serve as a clue for suspecting brain death. Its presence should call for full assessment of the patient with conventional diagnostic criteria to confirm or refute the diagnosis.

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