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NEW CSANZ GUIDELINES EMPHASISE
A “WHOLE OF LIFE” MANAGEMENT PLAN
FOR CONGENITAL HEART DISEASE (CHD):

• Every adult with repaired congenital heart disease should be seen at least once in an Adult Congenital Heart Disease centre1

• Every adult with unrepaired or non-simple* congenital heart disease should be seen regularly at an Adult Congenital Heart Disease centre1

The new CSANZ guidelines can be viewed and downloaded from the CSANZ website. A list of established Adult Congenital Heart Disease centres can be viewed at www.chdfindpah.com.au. This site is password protected – your login is: 3ndang3r3d

CSANZ: Cardiac Society of Australia and New Zealand. *Where simple CHD is small or repaired ASD, VSD or PDA without residual haemodynamic abnormality, or mild pulmonary or aortic valve disease.
Predictive testing: more than just another test

In this issue of the Journal, Wedderburn et al. describe their experience in the provision of a predictive testing service for neurodegenerative disorders. Following international guidelines, they describe their experience in a multidisciplinary clinic offering predictive testing for neurodegenerative disorders, such as Huntington disease. These disorders develop in adulthood and are mostly incurable. The predictive testing determines if a person will develop a disease many years before they start to show symptoms. To ensure acquiring such knowledge is in the patient’s best interest, international guidelines were developed when gene testing for Huntington disease became possible. These guidelines included a series of pretest supportive counseling interviews to protect the patient from finding out information that they could not cope with. This separated the process from diagnostic testing, where the patient was already symptomatic and the expectation of the patient having a disease was already subject of the doctor–patient relationship. This separation of the predictive testing from diagnostic testing resulted in many Australian laboratories refusing to process a DNA sample if it became obvious it was for a predictive test, unless the appropriate counselling accompanied it.

In the early days of developing the international protocol, there was great concern about the risk of the patient committing suicide if the gene testing of the pathogenic gene showed they had the mutated gene. Such a finding indicates that the person would develop Huntington disease or another neurodegenerative disease in the future. The incurable nature of such diseases lead to the concern about suicide; but fortunately, presumably because of the counselling protocols, many clinics have found suicide to be a rare event. This was also found by Wedderburn et al., who found no recorded evidence of major psychological reactions or suicides in their 740 at-risk patients. They also detailed why patients withdrew from the counselling process at various stages.

As the risk of suicide and severe psychological disturbance seemed much less than initially feared, many clinics have shortened the counselling process, although, most are able to provide in-depth counselling if required in special instances. The Huntington disease guidelines have been revised several times with the latest recommendations suggesting a less rigid approach as well as a more individualised approach. This is especially relevant for predictive testing for other genetic conditions. Such is the case for predictive testing for breast or bowel cancer where the counselling process may be only two or three visits depending on the needs of the individual. For adult onset conditions, the minimum age is usually set at 18 years of age, when the patient is judged to be an adult and can make their own decision. While it is very common for parents to demand genetic testing for their children for a variety of genetic conditions, the minimum age is usually set at 18 years. This is when the patient is judged to be an adult and capable of making an informed autonomous decision. A firmly established principle in genetic testing of children to wait until they are an adult. MacLeod et al. suggest that perhaps a more patient-centred approach be followed with adolescents who seek out predictive genetic testing themselves. For some specific conditions, the age limit does not apply when the disease has the potential to manifest in childhood or teenage years and preventative treatment is required. Such an example is familial adenomatous polyposis (FAP), which is known to manifest in the teenage years. Predictive counselling and testing are usually offered in early teenage years so that appropriate screening regimens can be put in place and appropriate preventative action can be taken. Furthermore, for conditions such as FAP, if detected early, treatment has a greater chance of success.

In cancer genetics specifically, genes are often variably penetrant and therefore even if a pathogenic gene is identified, there remains to be a level of uncertainty. For example, if a woman is found to be a carrier of a BRCA1 or BRCA2 gene, her lifetime risk of developing a breast cancer becomes 50–80%. This does not suggest that she will definitely develop breast cancer; however, her risk is now much higher than that of a woman in the general population. This gives her a number of choices, such as regular examination and mammography or prophylactic mastectomy. It is important that patients consider, prior to undertaking predictive testing, how they might cope with the knowledge that they are in a high-risk category. Pretest counselling is invaluable to the process of predictive testing and helps to assist patients with making the decision about whether they will go ahead with predictive testing at a particular point in their life, and whether the test will provide them with information that they feel...
will benefit them in the long run. Wedderburn et al. describe how in their experience, people most often chose to withdraw from the predictive testing process during this pretest counselling. Presumably, this is because the pretest counselling helps to illustrate the depth and significance the information provided and helped the patient to further reflect upon the impact this information might have on their lives.

For predictive testing, each case is unique and each individual patient learns of their potentially increased risk in different ways. Some people have little to no experience with the disease at hand, while others have an apparently extensive knowledge and experience with the disease in their family. People’s personal experiences are often a major determining factor in how they perceive situations that will inevitably influence their decision-making, and the actual lived experience of each individual patient is vastly different. With this in mind, it makes sense to approach predictive testing in a flexible, patient-centred manner using a team approach that includes professional with counselling skills. The current recommendations for the Huntington disease predictive testing guidelines recommend an individualised approach to the process of pretest and post-test counselling based on current evidence and expertise. Wedderburn et al.’s article on predictive gene testing for Huntington disease provides such evidence of current practice in a multidisciplinary setting.

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Hip fracture in Australia: missed opportunities and a chance to improve care

A hip fracture is a devastating event for an older person, with consequences that include pain, disability, loss of independence, institutionalisation and death. All too often, it represents the final stage of a 30-year journey manifest through decreasing bone strength and increasing falls risk. As 450 million baby boomers enter retirement, healthcare systems across the world must prepare to develop systematic approaches to hip fracture care and prevention.

In 2006–2007 there were 16 518 reported osteoporotic hip fractures in Australia. Or put in simpler terms and using the 2006–2007 data, there are approximately 40 new hip fractures a day in Australia, of which the large majority will be admitted to hospital and undergo surgical intervention. Two will die in the hospital and four will be new discharges to a residential aged care facility. A further six or seven will die in the following 12 months, and of those who survive, less than half will have regained their pre-fracture level of function a year after the fracture.

While the rate of hip fracture is decreasing in Australia, an Australian Institute of Health and Welfare report provides data to demonstrate a higher rate of hip fracture in
our Aboriginal and Torres Strait Islander populations with indigenous men twice as likely to fracture their hip when compared with non-indigenous males (RR 2.01, 95% CI 1.70–2.54). Indigenous women are also at increased risk of hip fracture (RR 1.26, 95% CI 1.07–1.47), and both male and female indigenous people are more likely to fracture at a younger age.

In this issue of the Journal, the article by Wong et al.4 provides confirmation of the higher rate of hip fracture in the indigenous population of Western Australia (WA), and shows a striking 7.2% annual increase in hip fracture contrast to a 3.4% annual decrease in hip fracture in non-indigenous adults in WA. This is also a population with a higher prevalence of diabetes and renal disease, and high levels of alcohol intake, all of which have the potential to impact on the rate of, as well as recovery from, a hip fracture.5 More research is required in Indigenous Australians to define better the relative contribution of health and lifestyle factors to this apparent difference in rate of hip fracture such that targeted interventions delivered in a culturally appropriate way can be developed for the future.

The impact of a hip fracture on an individual is substantial and is the main driver for improving preventive strategies. Much can be done to reduce falls and fractures in older people, with a substantial evidence base available to guide practice and shape intervention.6–11 The majority of hip fractures are as a result of a fall, and there are several different approaches to preventing falls in older people, which include exercise in the form of balance and strength training, reducing central nervous system medication use, vitamin D in people who are vitamin D deficient, occupational therapy home assessment, tailored foot care assessment and intervention, and avoidance of bifocal and multifocal glasses. The latest Cochrane reviews6,7 provide detailed systematic analysis of fall prevention strategies and high-quality summaries of which intervention is appropriate for which population.

There is also good evidence to support pharmacological interventions to reduce fracture risk in people with osteoporosis and those who have previously sustained a low-trauma fracture.8 Much of this evidence has been available for three decades, yet we are still to see widespread adoption of models of care that systematically identify and address fall and fracture risk. This is despite the significant efforts of many clinicians and associated professional bodies advocating for such approaches to be implemented. The development and evaluation of secondary fracture prevention services provides compelling data to support this approach as a way of delivering clinical and cost-effective care.8

While secondary fracture prevention services exist in several areas in Australia, the routine identification of people at high risk of future fracture and the subsequent implementation of appropriate intervention strategies is far from routine practice. Up to 50% of those 16 518 hip fractures in 2006–2007 will have previously sustained a low-trauma fracture, yet the reality is that the majority will not have been on any formal treatment for osteoporosis at the point of admission with their hip fracture.12–14 Our failure to systematise our models of care and provide treatments from which individuals stand to benefit leaves people exposed to substantial risk of an event that at a minimum will cause pain and disability, and at worst precipitate an early death.

In the event of a person sustaining a hip fracture and leading to hospitalisation, the quality of hip fracture care has been shown to be dependent upon orthopaedic and geriatric service configurations.15 In the absence of effective systems of orthopaedic-geriatric co-care, key markers of quality of care – including time to surgery, peri- and postoperative complication rates, readmission rates, and the length of stay – have been demonstrated to vary considerably.16

Across the world, professional organisations, patient societies and policymakers have recognised the need and opportunity to improve the quality of hip fracture care. In the UK, the development of a national registry (http://www.nhfd.co.uk) supported by evidence-based guidelines16 and agreed standards of care17 has led to a year-on-year improvement in several aspects of hip fracture care, which has ultimately also impacted significantly on 30-day mortality.

Moves are afoot in Australia and New Zealand to develop equivalent guidelines and standards of care, and for the implementation of these to be supported by an ongoing process of evaluation with the development of an Australian and New Zealand (ANZ) Hip Fracture Registry. An audit of all public hospitals across Australia and New Zealand that operate on hip fracture patients has recently been completed, and shows marked variation in several structures and processes of care for hip fracture patients, including the availability of orthogeriatric services, dedicated or scheduled trauma lists, and access to secondary fracture prevention services (http://www.anzhfr.org). Pilot work on patient-level data is also underway in both New South Wales and WA, with WA now utilising an electronic data collection system and a small financial incentive to support best practice based on the UK approach to care. The ANZ Guideline for Hip Fracture Care is due to be published in 2014.

While the costs to the individual from a hip fracture are self-evident, the cost to the Australian healthcare system should also be considered. In this issue, the article by Ireland and Kelly18 provides a timely reminder about the real costs of providing healthcare for those with a hip fracture.5 More research is required in Indigenous Australians to define better the relative contribution of health and lifestyle factors to this apparent difference in rate of hip fracture such that targeted interventions delivered in a culturally appropriate way can be developed for the future.
fracture. Much of the data that precede this work focus on the acute costs of care and fail to recognise the substantial subacute costs associated with rehabilitation following a fracture. We also fail to acknowledge the substantial social care and societal costs associated with debilitating conditions as these are often difficult to measure.

As the health system in Australia transitions into the world of activity-based funding, it is crucial that the use of linked data becomes commonplace so as to provide an accurate measurement of performance and address the potential to create an illusion of efficiency that fails to improve care, generate capacity or lead to cost-efficiencies in the healthcare system in its broadest sense.

Moving forward in Australia, it is critical that we take the core principles that underpin secondary fracture prevention, and apply these to models of care adapted for the local context and that take into account the challenges that geography, language and culture present in Australia. Equally, for those that are unfortunate enough to fracture their hip, the care they receive should reflect the evidence base so as to maximise the chances of survival and meaningful recovery.

At some stage, we will embrace the reality that high-quality care costs less and recognise that upfront investment is required to put in place the necessary infrastructure and services to support secondary fracture prevention and deliver first-class hip fracture care to all Australians.

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CLINICAL PERSPECTIVES

Advances in the management of hepatitis C
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Key words
hepatitis C, management, triple therapy, protease inhibitors, fibroscan, IL28B genotype.

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Abstract
Significant advances have recently been made in the management of hepatitis C virus (HCV) with many of the changes now part of routine clinical practice. These include the use of non-invasive methods to assess liver fibrosis, interleukin 28B genotype testing to predict interferon responsiveness and the use of new anti-viral regimens for HCV genotype 1. Two new antiviral agents (boceprevir and telaprevir) have recently become available in Australia. These protease inhibitors are used in combination with pegylated interferon and ribavirin as triple therapy for genotype 1 HCV. This combination increases sustained virological response from approximately 45–50% to 66–75% in treatment naïve patients. However, these new regimens present novel challenges including complicated treatment algorithms based on virological response, numerous drug interactions and additional side effects especially in patients with advanced fibrosis. The protease inhibitors are the first of many antiviral drugs to become available to treat HCV, heralding the arrival of new agents that will offer greater chances of cure with improved safety and tolerability compared with current therapies.

Introduction
Chronic hepatitis C virus (HCV) infection remains a major public health problem in Australia. Acute infection leads to chronicity in 75% of cases. The important complications of HCV include cirrhosis, liver failure and hepatocellular carcinoma (HCC). An estimated 226 700 people in Australia are infected with HCV including 49 500 with moderate to severe liver disease.1 The burden of disease due to complications of cirrhosis and HCC is predicted to increase over the next 20 years. Currently, HCV is the most common indication for liver transplantation in Australia accounting for 22% of transplants in adults.2 Over the course of the past 20 years, the management of HCV has evolved from the use of standard interferon monotherapy to interferon and ribavirin dual therapy, and then in 2003, the introduction of pegylated (long-acting) interferon (Peg IFN). In particular, over the past 3–4 years, there have been significant and rapid advances in various aspects of the management of HCV, many of which are now in routine clinical practice in Australia. These have included new diagnostic tests to predict liver fibrosis and response to treatment and several new direct acting anti-viral drugs.

In this article, we provide an overview of the public health and clinical problem of HCV in Australia and summarise some of the new diagnostic tests and therapeutic approaches available to patients with HCV.

HCV: epidemiology in Australia

There are an estimated 10 000 new HCV infections per year in Australia and the major risk factor for acquiring HCV is injecting drug use (IDU).1 A reduction in HCV incidence among injecting drug users attending needle and syringe programs has been shown over the past decade. Approximately 11% of patients with chronic HCV in Australia are immigrants3 and may have acquired the virus in their country of birth through non-sterile medical practices including blood transfusions, injections with contaminated syringes, dental or other surgery, acupuncture or traditional practices such as tattooing. The genotype distribution of HCV in Australian populations has been reported as follows: genotype 1 (52%), 2 (9%), 3 (31%), 4 (5%), 6 (2%) and mixed (1%).3 Genotype distributions vary in different parts of the world and have significance for response to treatment (e.g. genotype 3 responds better to Peg IFN and ribavirin than genotype 1) and also for the applicability of certain new tests (interleukin (IL)28B) and drugs. Due to the ageing of the large cohort of HCV patients who acquired HCV through IDU in the 1980s and 1990s, the liver related morbidity associated
with the virus is due to escalate over the next 10–20 years. It is thought that 85% of HCV cases in Australia have been diagnosed; however, despite a slow increase in treatment uptake over the years (an estimated 1847 HCV patients treated in 2005 and 3562 in 2008), the overall rate of treatment uptake remains low (<2% per year). Numerous barriers to treatment uptake exist including lack of knowledge about HCV and its treatments both in clinicians and patients, the long, difficult nature of IFN-based treatments and social instability psychiatric comorbidities and ongoing drug and alcohol dependency in some patients.

The provision of better education and support to patients (both socially and for drug and alcohol addictions) and practitioners (GP and drug and alcohol physicians) and increased capacity for assessment and treatment especially in drug and alcohol settings have been suggested. In the third national Hepatitis C Strategy for 2010–2013, several priority groups have been identified for targeted intervention in order to prevent new infections and to increase access to treatment. These include people who inject drugs, people of Aboriginal and Torres Strait Islander background, people in custodial settings (in whom the prevalence of HCV is approximately 40%) and those from culturally and linguistically diverse backgrounds.

**Hepatitis C infection: clinical sequelae**

Although chronic infection with HCV is usually asymptomatic, patients may report non-specific symptoms, in particular fatigue, anorexia or arthralgia even in the absence of significant liver disease. However, it is the development of cirrhosis and its complications that represent the most important adverse outcomes of HCV infection. Estimates of the rates of cirrhosis have varied considerably in natural history studies depending on the cohort studied. For example, in a community-based cohort of women infected through contaminated Rhesus immune globulin, cirrhosis was present in less than 5% after 15–20 years of follow-up compared with patients with transfusion associated hepatitis C in whom up to 50% developed cirrhosis. The risk of cirrhosis is influenced by several factors including age at infection (older age at infection results in higher cirrhosis rates), male gender, immunosuppression (especially due to post-transplant medications and HIV co-infection) and the presence of other hepatotoxic cofactors including heavy alcohol use, hepatitis B or non-alcoholic steatohepatitis.

The risk of decompensated liver disease with ascites, encephalopathy, jaundice or bleeding from varices is thought to occur at a rate of 2–4% per year in patients with HCV-related cirrhosis. Hepatocellular carcinoma is the other major cause of mortality in patients with HCV and develops in those with cirrhosis at a rate of 1–7% per year. Consequently, regular screening with 6-monthly liver ultrasound is recommended in patients infected with HCV who have advanced fibrosis or cirrhosis (Metavir fibrosis stage 3 and 4).

**Assessment of hepatitis C**

**Transient elastography (TE) and other non-invasive tests of fibrosis (Table 1)**

Until 2006, liver biopsy was a pre-requisite for HCV antiviral therapy. Although there are still situations in which a biopsy is needed to help clarify the aetiology of liver disease and accurately determine the extent of fibrosis, the removal of this requirement has resulted in far fewer liver biopsies being performed. In hepatitis C, significant treatment decisions including the urgency for antiviral

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<tbody>
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<td>Blood test which identifies genetic polymorphisms associated with the interleukin-28B gene (recently renamed IFN lambda 3). Genotype predicts responsiveness to Interferon therapy.</td>
</tr>
<tr>
<td>Fibroscan (transient elastography)</td>
<td>Non-invasive, ultrasound-based measure of liver stiffness used to predict the presence of minimal fibrosis or cirrhosis. Expressed in kilopascals (kPa).</td>
</tr>
<tr>
<td>Acoustic radiation force impulse (ARFI) imaging</td>
<td>Ultrasound-based measure, expressed in meters/second with strong correlation with degree of fibrosis as assessed on liver biopsy.</td>
</tr>
<tr>
<td>Hepascore</td>
<td>Non-invasive measure using serum markers including bilirubin, gamma glutamyl transferase, hyaluronic acid, alpha 2 macroglobulin, age and sex. Can provide useful information about fibrosis stage.</td>
</tr>
<tr>
<td>Fibrotest/Fibrosure</td>
<td>Involves assessment of 6 serum markers (alpha-2-macroglobulin, alpha-2-globulin (haptoglobin), gammaglobulin, apolipoprotein A1, gamma glutamyl transferase, and total bilirubin) age, and sex and is widely used in the USA and Europe.</td>
</tr>
<tr>
<td>APRI score</td>
<td>The Aspartate aminotransferase (AST) to platelet ratio index. Easy to calculate and is most useful for excluding significant fibrosis in HCV.</td>
</tr>
</tbody>
</table>
treatment and also duration of treatment are influenced by the stage of fibrosis. For example, patients with genotype 2/3 are usually only treated with Peg IFN and ribavirin for 24 weeks but this is extended to 48 weeks in those with advanced fibrosis. The advent of non-invasive ultrasound-based technology (TE or acoustic radiation force impulse imaging (ARFI)) allows an estimation of liver fibrosis by liver stiffness measurement (LSM). The Fibroscan (Echosens, Paris, France) is a device that utilises TE to determine liver stiffness and is now widely used in larger hospitals throughout Australia and Europe. It is a simple and rapid test, performed at the bedside usually by a doctor. Fibroscan uses a specialised probe placed on the skin over the right upper quadrant, which generates a small impulse or vibration/shear wave that is propagated through the liver. The velocity of the shear wave corresponds to the degree of liver stiffness, which in turn correlates with the degree of underlying liver fibrosis. Livers with significant fibrosis are stiffer and conduct impulses faster resulting in a higher stiffness score measured in kilopascals. The optimal cut-off values for the presence of significant fibrosis (stage F2 or greater) and cirrhosis suggested in a large meta-analysis of 50 studies were 7.6 and 13.0 kPa respectively. Fibroscan has some limitations, for example, fibrosis may be overestimated in patients with significant liver inflammation with elevated alanine aminotransferase levels and when there is significant congestion in the liver, and may be difficult to obtain in patients who are obese, have narrow intercostal spaces or ascites. ARFI is another ultrasound-based, non-invasive test that uses shear wave velocity quantification to measure liver stiffness and is comparable with Fibroscan for predicting significant fibrosis/cirrhosis. It is not influenced by serum ALT concentration. Several other non-invasive diagnostic tools, which use serum tests as well as demographic features to predict fibrosis stage are also available, including the Hepascore, Fibrotest and APRI score (Table 1), although these vary in diagnostic accuracy. The Hepascore was developed by investigators in Western Australia and utilises various biomarkers of fibrosis, including Alpha 2-macroglobulin and hyaluronic acid levels, as well as bilirubin and gamma glutamyl transferase (GGT) in addition to age and sex. A hepatoscore of 20.50 is 89–92% specific for the presence of F3/F4 fibrosis, and a score of >0.84 is 84–89% specific for the presence of cirrhosis. However, the lack of easy access to some of the tests restricts their use in certain settings. Another of the current limitations of non-invasive tests is their inability to distinguish between intermediate stages of fibrosis. Overall, however, the increasing availability of non-invasive tests of fibrosis represent a significant advance in providing critical information to clinicians without exposing patients to the risks of liver biopsy.

**IL28B genotype**

The responsiveness of HCV genotype 1 patients to dual therapy with Peg IFN and Ribavirin was recently found to be strongly predicted by genetic polymorphisms in the region of the IL28B gene on chromosome 19. The IL28B gene encodes interferon lambda, which is upregulated by interferons and also plays a role in the innate immune response to HCV. Using genome-wide association studies, single nucleotide polymorphisms were identified and correlated with clinically significant outcomes. In particular genotype 1 patients with favourable IL28B genotypes (either at the rs12979860 or rs8099917 sites) have increased sustained virological response (SVR) rates with Interferon treatment. The alleles in this region occur with varying frequency in different racial groups and this is now thought to be part of the explanation for the variation in SVR observed between patients of Asian, Caucasian and African origin. The IL28B genotype has been useful in making decisions about treatment and pre-therapy counselling of patients about their chances of successful eradication.

**Protease inhibitors with Peg IFN and ribavirin (triple therapy) for genotype 1 hepatitis C**

**Increased response rates**

In April 2013, the protease inhibitors, telaprevir (Incivo, Janssen-Cilag Pharmaceuticals, Sydney, NSW, Australia) and boceprevir (Victrelis, Merck, Sharp and Dome, Sydney, NSW, Australia) gained Pharmaceutical Benefits Scheme approval in Australia for use in combination with Peg IFN and ribavirin for genotype 1 HCV. These drugs inhibit the action of the HCV NS3/4a serine protease (involved in the processing of HCV polyproteins) and are only licensed for use in genotype 1 infections because of limited activity against other genotypes. Persistent clearance of virus for 6 months (24 weeks) after therapy has been completed is termed ‘sustained virological response’ (SVR or SVR24), and this accurately predicts long-term cure. Several phase 3 trials published in 2011 demonstrated improved SVR with triple therapy compared with Peg IFN and ribavirin alone (Fig. 1). An improvement in SVR rates (of approximately 30% overall) was seen in both treatment naïve patients and patients who had prior relapse or partial response (see Table 2 for definitions). Shortened courses of therapy...
Response-guided therapy (RGT) are possible in a significant number of non-cirrhotic patients (44–65%) that have undetectable HCV RNA at key time points, and these patients achieve very high SVR rates (87–97%). Eligibility for RGT are summarised in Table 3.

Treatment algorithms differ depending on which protease inhibitor is used. Telaprevir is given for the initial 12 weeks in combination with Peg IFN and ribavirin followed by a variable period of dual therapy (24 or 48 weeks total therapy). Boceprevir is added after a 4-week lead-in period of Peg IFN and ribavirin dual therapy and is given for variable durations (24–44 weeks) depending on prior treatment experience and on-treatment response. Several stopping rules (Table 3) have been developed to avoid unnecessarily treating patients in whom viral clearance is unlikely to occur and in whom resistance has developed. It is worth noting that the futility rules used in Australia differ slightly from those in North America.

**Additional treatment related issues in triple therapy**

Treatment with Peg IFN is commonly associated with a myriad side-effects that include lethargy, insomnia, flu-like symptoms (arthralgia, myalgia, fever), depression, irritability, cytopenias (anaemia, neutropenia and thrombocytopenia), rash, hair loss, nausea, anorexia and weight loss, and thyroid abnormalities. Ribavirin is associated with haemolytic anaemia and importantly is teratogenic and is therefore contraindicated in pregnancy or in men whose partners are pregnant or are planning pregnancy. Protease inhibitor-based triple therapy involves several additional toxicities to those seen with Peg IFN and ribavirin dual therapy. Anaemia was reported in up to half of patients treated with boceprevir triple therapy but can usually be managed with ribavirin dose reduction without impacting on the SVR rates. Rash occurs in about 50% of patients on telaprevir. Although generally mild, severe and sometimes life-threatening skin reactions can occur with cases of Stevens Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome having been described. Dysgeusia (altered taste sensation) with boceprevir and anorectal symptoms with telaprevir are other reported side-effects.

The dosing schedule for telaprevir and boceprevir is demanding because medication must be taken with high fat meals or snacks to improve bioavailability. The protease inhibitors are eliminated by cytochrome P450 3A4/5 (CYP3A4/5) enzymes involved in drug metabolism. Thus, co-administration of drugs that induce CYP3A4/5 can reduce the concentrations of boceprevir or telaprevir. Strong inducer drugs include anticonvulsants, certain antibiotics (rifampicin and some anti retroviral drugs for HIV) and importantly the herbal preparation St John’s wort. The protease inhibitors are also potent inhibitors of CYP3A4/5 and therefore may increase the concentrations of drugs that are dependent on the CYP3A4/5 for metabolism. Table 4 provides a list, although by no means exhaustive, of some of the important drug interactions.

**Table 2** Commonly used terms in HCV treatment

- **RVR**: rapid virological response. HCV RNA negative at week 4 of therapy and up till end of therapy.
- **EVR**: early virological response. HCV RNA detectable at Week 4 but undetectable at week 12 of therapy (complete EVR) and up to end of therapy.
- **Partial response**: ≥2 log decline in HCV RNA by week 12 of therapy but with detectable RNA at weeks 12 and 24.
- **Null Response**: <2 log decline in HCV RNA by week 12 of therapy.
- **EoTR**: End of Treatment Response. Negative HCV RNA at completion of therapy.
- **Relapse**: HCV RNA negative at end of treatment but reappearance within 6 months.
several useful websites where potential drug interactions may be checked including at http://www.hep-druginteractions.org, and clinicians need to be vigilant about co-prescribing. Monitoring for increased toxicity or reduced efficacy of drugs with known interactions and dose adjustments before, during and after protease inhibitor therapy in such drugs may be required. Protease inhibitors are not able to be dose reduced and should never be used as monotherapy because drug-resistant HCV variants can emerge rapidly.

**Difficult to treat populations**

There remain certain populations with HCV, whose prospects of cure are diminished even with the use of protease inhibitor-based triple therapy for genotype 1 patients. These include those with previous null-response to therapy, genotype 1a (compared with 1b) and those with higher viral loads and advanced fibrosis. Treatment of patients with cirrhosis is particularly difficult because of pre-existing thrombocytopenia and neutropenia and the possibility of decompensation on therapy. A large French study of 497 patients with compensated cirrhosis found a 4.8% rate of severe infections, a 2.4% rate of hepatic decompensation and a 1% death rate (six patients). The authors noted that a platelet count ≤100 000/mm³ combined with a serum albumin ≤35 g/L were predictors of poor outcome; thus, patients with these markers should be treated with extreme caution and preferably in consultation with a liver transplant unit.

<table>
<thead>
<tr>
<th>Futility/Stopping rules</th>
<th>Telaprevir</th>
<th>Boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA &gt;1000 IU/mL at week 4 or</td>
<td>HCV RNA detectable at week 24 in all treatment naïve patients</td>
<td></td>
</tr>
<tr>
<td>HCV RNA detectable at week 12 or</td>
<td>HCV RNA detectable at week 12 or 24 in all treatment experienced</td>
<td></td>
</tr>
<tr>
<td>HCV RNA detectable at week 24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eligibility for shortened</th>
<th>Telaprevir</th>
<th>Boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA undetectable at weeks 4 and</td>
<td>HCV RNA undetectable at weeks 8 and 24 in treatment naïve patients</td>
<td></td>
</tr>
<tr>
<td>12 in treatment naïve patients and prior relapsers (prior partial responders also excluded from RGT)</td>
<td>HCV RNA undetectable at weeks 8, 12 in treatment experienced patients</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3** Futility rules and eligibility for shortened (response guided) therapy (RGT)

### Table 4 Sample list of some drugs with interactions with HCV protease inhibitors Boceprevir and Telaprevir

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug examples</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, Phenytoin</td>
<td>Reduced serum concentration of Protease inhibitor (PI). Coadministration contraindicated.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Rifampin, Rifabutin, certain HIV antiretrovirals</td>
<td></td>
</tr>
<tr>
<td>Other (Strong inducers of CYP3A)</td>
<td>Bosentan, Dexamethasone, St John’s wort.</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>Buprenorphine and Methadone</td>
<td>Variable effect with increased or decreased opioid concentration in Boceprevir and reduced Methadone concentration with Telaprevir</td>
</tr>
<tr>
<td>Oestrogen/Progestogen</td>
<td>Ethinyl estradiol, mestranol, levonorgestrel, medroxyprogesterone</td>
<td>Serum concentrations of ethinyl estradiol may be reduced by PI’s and levels of serum progestogens may be altered causing failure of hormonal contraception.</td>
</tr>
<tr>
<td>Hormonal contraception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-fungals</td>
<td>Itraconazole, Ketoconazole</td>
<td>May increase serum concentration of PI and of azole antifungals.</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Clarithromycin, Erythromycin</td>
<td>Risk of increased exposure to these drugs and their side effects if used concurrently with protease inhibitors</td>
</tr>
<tr>
<td>Anti-coagulants</td>
<td>Warfarin, Rivaroxaban, Dabigatran</td>
<td></td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>Amiodarone, Digoxin, Flecaïnide</td>
<td></td>
</tr>
<tr>
<td>Calcium channel antagonists (CCAs)</td>
<td>Amiodipine, Feli-dipine, Nicardipine</td>
<td></td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors (Statins)</td>
<td>Atorvastatin, Lovastatin, Simvastatin</td>
<td></td>
</tr>
<tr>
<td>GI Motility agents</td>
<td>Cisapride and Domperidone</td>
<td></td>
</tr>
<tr>
<td>Anti-gout</td>
<td>Colchicine</td>
<td></td>
</tr>
<tr>
<td>Calcineurin Inhibitors</td>
<td>Cyclosporine, Tacrolimus,</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Citalopram, Mirtazapine, Valfaxine</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Alprazolam, Clonazepam</td>
<td></td>
</tr>
<tr>
<td>Hynotics</td>
<td>Zopiclone, Zopiclone</td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase-5 Inhibitors</td>
<td>Sildenafil</td>
<td></td>
</tr>
</tbody>
</table>
in those who are potential liver transplant recipients. Patients with psychiatric comorbidities or ongoing drug dependency remain a challenge to treat. Currently with newer and better therapies on the horizon, the critical decision in many patients, especially those with advanced cirrhosis, is whether they should be treated now or deferred until more potent and less toxic therapies become available.

**Future directions**

There is a burgeoning field of direct acting antivirals for HCV with several drugs being tested in phase 2 and 3 clinical trials. In addition to protease inhibitors, other broad classes of drug include the NS5B polymerase inhibitors (nucleoside and non-nucleoside), inhibitors of the viral NS5A protein (which is involved in viral replication) and other viral proteins, as well as drugs which act on host factors required by HCV during its life cycle (e.g. cyclophilin inhibitors). Numerous next-generation protease inhibitors show promise for genotype 1 HCV in combination with Peg IFN and ribavirin including danoprevir, faldaprevir and simeprevir. Sofosbuvir is an oral, once-daily NS5B nucleotide analogue inhibitor with pan-genotypic activity which shows great promise in the treatment of HCV. An open-label study of 12 weeks of sofosbuvir, Peg IFN and ribavirin in a predominantly genotype 1, treatment naive population showed 90% of patients had undetectable virus 12 weeks post-treatment (12-week SVR or SVR12 which has become an accepted end-point for clinical trial reporting). A further trial of an IFN-free regimen using faldaprevir and deleobuvir plus ribavirin for 16, 28 or 40 weeks in genotype 1 treatment naïve patients found an overall 12-week SVR of 51–69%. In genotypes 2 and 3, a non-inferiority trial for treatment naïve patients comparing 12 weeks of sofosbuvir and ribavirin to standard of care therapy for 24 weeks showed that overall 12-week SVR rates were identical in both arms at 67%, thus providing an attractive alternative for those in whom interferon-based treatment may be unsuitable. Response rates in genotype 2 were higher at 93% than in genotype 3 (56%). A study of treatment experienced genotypes 2 and 3 relapers showed that sofosbuvir/ribavirin given for 16 weeks was significantly more effective than 12 weeks (SVR12 73% vs 50%). Numerous other combinations of three or four different antivirals in interferon-free regimes are also being tested in genotype 1 HCV. The rapid evolution of therapeutic agents in HCV brings its own challenges including the prevention of resistance, applicability of regimens to difficult to treat patients including prior null-responders and ensuring that 12-week SVR is equivalent to 6-month SVR and that the end-point SVR24 remains equitable with cure with late relapses being rare.

**Conclusions**

We are entering an exciting era of HCV treatment. Novel diagnostic tools enable non-invasive assessment of the severity of fibrosis, and the addition of the protease inhibitors to our armamentarium offers higher rates of SVR to genotype 1 patients, often with shortened durations of therapy. Clinicians are adapting to complicated treatment algorithms that depend on knowledge of prior interferon experience, on-treatment response and extent of hepatic fibrosis. There are many new drugs in the process of development that show great promise and the era of interferon-free therapies for hepatitis C is on the horizon although the exact timing of this ‘new dawn’ remains uncertain. In patients with minimal fibrosis deferring treatment until the advent of eagerly anticipated potent, new therapeutic agents may be safe. However, in those with cirrhosis, the immediate future still represents a period of uncertainty in which the risks of undergoing protease inhibitor-based therapies have to be weighed against the risks of progressive liver disease.

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Predictive gene testing for Huntington disease and other neurodegenerative disorders

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Key words
predictive gene testing, Huntington disease, neurodegenerative disorder.

Abstract

Background: Controversies exist around predictive testing (PT) programmes in neurodegenerative disorders.

Aims: This study sets out to answer the following questions relating to Huntington disease (HD) and other neurodegenerative disorders: differences between these patients in their PT journeys, why and when individuals withdraw from PT, and decision-making processes regarding reproductive genetic testing.

Methods: A case series analysis of patients having PT from the multidisciplinary Western Australian centre for PT over the past 20 years was performed using internationally recognised guidelines for predictive gene testing in neurodegenerative disorders.

Results: Of 740 at-risk patients, 518 applied for PT: 466 at risk of HD, 52 at risk of other neurodegenerative disorders – spinocerebellar ataxias, hereditary prion disease and familial Alzheimer disease. Thirteen per cent withdrew from PT – 80.32% of withdrawals occurred during counselling stages. Major withdrawal reasons related to timing in the patients’ lives or unknown as the patient did not disclose the reason. Thirty-eight HD individuals had reproductive genetic testing: 34 initiated prenatal testing (of which eight withdrew from the process) and four initiated pre-implantation genetic diagnosis. There was no recorded or other evidence of major psychological reactions or suicides during PT.

Conclusions: People withdrew from PT in relation to life stages and reasons that are unknown. Our findings emphasise the importance of: (i) adherence to internationally recommended guidelines for PT; (ii) the role of the multidisciplinary team in risk minimisation; and (iii) patient selection.

Introduction

Predictive genetic testing for Huntington disease (HD) has been available for longer than any other genetic disease,1 and predictive testing (PT) is now available for a range of other conditions, such as the spinocerebellar ataxias (SCA), hereditary prion disease and familial Alzheimer disease (AD). There are many types of PT, and for the purposes of this paper, these can be differentiated into three broad categories: at an individual level, at a prenatal level and at the pre-implantation of an embryo. Prior to 1993, individuals at risk of HD could undergo testing through linkage analysis.2 With the identification of the CAG trinucleotide repeat region PT involves only the at-risk individual, and a result is provided with almost 100% accuracy.3,4 The alternative to PT is diagnostic testing (DT). For DT to take place, an individual should be symptomatic or perceived to have symptoms of HD, and then referred to a neurologist who will use the Unified Huntington Disease Rating Scale (UHDRS)5 to determine if there is a clinical diagnosis of HD to be made or not.

The PT programme follows international guidelines as recommended by the International Huntington Association and the World Federation of Neurology6,7 and was modified by an international committee after the discovery of gene mutation in 1993.8 The testing involves several sessions: (i) initial contact and pre-screen interview with the at-risk individual; (ii) at least three pretest in-person sessions for genetic and psychological counselling, and neurological and neuropsychological evalu-
At risk of HD. It also asks the reasons for withdrawal and main motivating factors in over one third of individuals children; reproductive decision-making is one of the asking how PT influences life decisions, such as having an affected foetus.

The results are disclosed at the following session, usually about 1 month after the blood is drawn; (v) posttest counselling sessions – the number determined by the needs of each patient. A similar process is performed in prenatal testing. PT is offered to asymptomatic individuals who, based on their family history, are at risk of developing the disorder and differs from DT, in which a person is displaying symptoms and has physical signs suggestive of a particular genetic disorder.

Prenatal testing is used to detect changes in a foetus' genes before birth and is usually performed using chorionic villus sampling during the first trimester; it is offered to couples with increased risk of having an affected foetus – prenatal testing can assist couples to decide whether to keep or abort the foetus. Pre-implantation genetic diagnosis (PGD) is performed on embryos prior to implantation, as part of the in vitro fertilisation procedure; usually, a cell is extracted from the embryo at the eight cell stage and genetically analysed – this avoids the implantation of an affected foetus.

This study sets out to investigate the controversies by asking how PT influences life decisions, such as having children; reproductive decision-making is one of the main motivating factors in over one third of individuals at risk of HD. It also asks the reasons for withdrawal and at what stage of the PT process. A previous study made a comparison of the variability in the number of withdrawals from PT and in the stages of withdrawal, but was unable to analyse appropriately the reasons for withdrawal. This study compares its findings with those of others, and attempts to determine the personal reasons of patients withdrawing from PT. We also sought information on any differences that there might be between HD and other neurodegenerative disorders in progress through PT. We also studied individuals having reproductive genetic testing: prenatal testing and PGD in HD.

Methods

This study is a retrospective case series analysis of patients having PT over the past 20 years at a Western Australian centre for predictive gene testing located at the Neurosciences Unit Health Department of Western Australia. A multidisciplinary team comprising a consultant neurologist, psychiatrist, neuropsychologists, counselling psychologists, social workers, speech and language therapists, geneticists, and a molecular biochemist work together in the management of patients at risk, or who have HD or other neurodegenerative disorders. PT was performed using the guidelines recommended by the World Federation of Neurology. Patients can either undergo PT or DT for a condition. DT is when a clinical diagnosis is made by a neurologist, and in HD using the UHDRS. The Neurosciences Unit is the Western Australian centre for gene testing for neurodegenerative disorders, where our team and our neurologist diagnose and manage HD and most other genetic neurodegenerative disorders; the DT results arise from this experience and help place PT in context. Computerised database records date from 1981 to current day, and provide information regarding the DT and PT status of individual patients. A patient’s status is recorded as pending, results given or withdrawn if they have left the programme. The database records are those of patients at risk of HD or other neurodegenerative disorders who have been referred to the Neurosciences Unit for assessment and who gave consent for their details to be used by the Neurosciences Unit for research purposes. Ethical approval was granted by the North Metropolitan Area Health Service, Mental Health Human Research Ethics Committee (September 2011).

Data collection

The HD database, which had a total of 740 individuals on record, was considered first as a whole and then narrowed down to specific sections. The data were divided into three sections: PT (68%), DT (21%) and discounted (11%). The discounted section comprised patients who lacked appropriate data for analysis in the HD database: absence of a PT or DT status, or unrecorded sex are examples. Basic demographic data (age range, mean age and the percentage of males to females) were calculated for PT, DT and discounted data combined, then PT and DT combined, and finally for PT and DT separately. The number of patients with a withdrawn status for PT or DT was then calculated for comparison. This process was then applied to the other neurodegenerative disorders database. Figure 1 illustrates a flow diagram of how the number of withdrawn PT patients was derived for HD and other neurodegenerative disorders. Of the patients with other neurodegenerative disorders, patients with familial prion disease had Creutzfeldt–Jakob disease with the codon E200K mutation; patients with familial AD had a PSEN1 5.9kb deletion mutation on exon 9; and SCA patients had SCA 1, 2, 3, 6 and 7.

The medical records for each patient were examined to determine the reason for withdrawing from the PT programme and at what stage of the PT process. Where a reason could not be identified from the medical records, the case managing social worker was interviewed to determine a withdrawal reason. In a few cases, this involved the case managing social worker to recall events...
that had occurred over a decade ago, but this did not mean that the patient had not been in contact with them, or the Neurosciences Unit, for that length of time. In the event that a reason could not be identified, this was recorded as unknown, despite a thorough attempt to do so, short of interviewing the patients – not allowed by our ethics committee for fear of precipitating an adverse psychological reaction. Reasons for all of the other withdrawals were recorded. Demographic data from the reproductive genetic testing databases consisted of the sex of the affected individual and the number of gene positive and negative pregnancies, along with the number of terminations.

Statistical analysis

Demographic data, such as mean age, percentages of males to female and standard deviations, were calculated using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA). Statistical analyses, such as 95% confidence intervals, standard error of mean values, along with contingency tables and specific tests such as Fisher’s exact test and chi-square test, were calculated using GraphPad InStat program (version 3.0 for Windows, InStat Software, La Jolla, CA, USA; http://www.graphpad.com).

Results

Demographics

Of 740 patients recorded on the computerised database, a total of 518 individuals (70%) applied for the PT process: 466 (90%) were individuals at risk of HD and 52 (10%) were individuals at risk of other neurodegenerative disorders: SCA, familial prion disease and familial AD (Tables 1 and 2).

PT analysis

As the majority of the PT individuals were from the HD group, as there were more data pertaining to these individuals, a more in-depth analysis was performed. First, the number of PT results given out over the last 20

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Population for predictive and diagnostic gene testing for Huntington disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington disease</td>
<td>n</td>
</tr>
<tr>
<td>PT/DT/disc</td>
<td>640</td>
</tr>
<tr>
<td>PT/DT</td>
<td>621</td>
</tr>
<tr>
<td>PT</td>
<td>466</td>
</tr>
<tr>
<td>DT</td>
<td>132</td>
</tr>
</tbody>
</table>

CI, confidence interval; disc, discounted; DT, diagnostic testing; PT, predictive testing; SD, standard deviation.
years was analysed (Fig. 2). Three hundred and seventy-three individuals had a CAG repeat length recorded on the database as a result of PT, and the distribution of these results was as follows: 216 had \( \leq 26 \) repeats on both alleles, 3 had 27–35 repeats on one allele, 13 had 36–39 repeats on one allele, and 125 \( \geq 40 \) repeats on one allele. Thirteen had no CAG repeat length recorded. Of these individuals, 215 (57.64%) were female and 158 (42.35%) were male.

The mean and median ages at PT and diagnosis of HD were calculated for each CAG repeat length of individuals who went through the PT programme and subsequently developed a diagnosis of HD (Table 3, Fig. 3a). The interval in years between patients having PT and subsequently diagnosed with HD was also determined (Fig. 3b). These patients had recorded dates of PT results and dates of diagnosis. Not every patient in the database had both of these dates recorded, and so they were not included in this particular part of the analysis.

**Withdrawal analysis**

Analysis of PT withdrawal reasons was done in both groups. The proportion of withdrawals for each group

<table>
<thead>
<tr>
<th>CAG repeat length</th>
<th>n</th>
<th>Median age at PT</th>
<th>Mean age at PT ± 1 SD</th>
<th>95% CI for mean age at PT</th>
<th>Median age at clinical diagnosis</th>
<th>Mean age at clinical diagnosis ± 1 SD</th>
<th>95% CI for mean age at clinical diagnosis</th>
<th>Mean interval between PT and clinical diagnosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>2</td>
<td>62.0</td>
<td>62.0 ± 2.8</td>
<td>36.8–87.2</td>
<td>64.5</td>
<td>64.5 ± 4.9</td>
<td>20.5–108.5</td>
<td>2.5</td>
</tr>
<tr>
<td>39</td>
<td>1</td>
<td>68.0</td>
<td>68.0 ± 0.0</td>
<td>—</td>
<td>68.0</td>
<td>68.0 ± 0.0</td>
<td>—</td>
<td>0.0</td>
</tr>
<tr>
<td>40</td>
<td>1</td>
<td>58.0</td>
<td>58.0 ± 0.0</td>
<td>—</td>
<td>60.0</td>
<td>60.0 ± 0.0</td>
<td>—</td>
<td>2.0</td>
</tr>
<tr>
<td>41</td>
<td>1</td>
<td>35.0</td>
<td>35.0 ± 0.0</td>
<td>—</td>
<td>48.0</td>
<td>48.0 ± 0.0</td>
<td>—</td>
<td>13.0</td>
</tr>
<tr>
<td>42</td>
<td>8</td>
<td>51.0</td>
<td>53.1 ± 10.0</td>
<td>44.7–61.4</td>
<td>56.5</td>
<td>57.4 ± 7.3</td>
<td>51.3–63.5</td>
<td>4.3</td>
</tr>
<tr>
<td>43</td>
<td>7</td>
<td>45.0</td>
<td>47.3 ± 12.9</td>
<td>35.4–59.2</td>
<td>53.0</td>
<td>54.0 ± 9.4</td>
<td>45.3–62.7</td>
<td>2.7</td>
</tr>
<tr>
<td>44</td>
<td>4</td>
<td>42.0</td>
<td>45.3 ± 9.0</td>
<td>31.1–59.7</td>
<td>44.5</td>
<td>46.5 ± 8.3</td>
<td>33.3–59.7</td>
<td>1.2</td>
</tr>
<tr>
<td>45</td>
<td>5</td>
<td>27.0</td>
<td>30.2 ± 8.3</td>
<td>19.9–40.5</td>
<td>39.0</td>
<td>39.8 ± 2.0</td>
<td>37.3–42.3</td>
<td>9.6</td>
</tr>
<tr>
<td>46</td>
<td>6</td>
<td>36.5</td>
<td>33.5 ± 6.8</td>
<td>26.4–40.6</td>
<td>43.5</td>
<td>41.2 ± 8.3</td>
<td>32.5–49.9</td>
<td>7.7</td>
</tr>
<tr>
<td>47</td>
<td>2</td>
<td>31.5</td>
<td>31.5 ± 6.4</td>
<td>−26.0–89.0</td>
<td>36.5</td>
<td>36.5 ± 2.1</td>
<td>17.6–55.4</td>
<td>5.0</td>
</tr>
<tr>
<td>48</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>49</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>50</td>
<td>1</td>
<td>19.0</td>
<td>19.0 ± 0.0</td>
<td>—</td>
<td>35.0</td>
<td>35.0 ± 0.0</td>
<td>—</td>
<td>16.0</td>
</tr>
</tbody>
</table>

ANOVA between CAG repeat length and mean ages at PT and clinical diagnosis by a neurologist using the Unified Huntington Disease Rating Scale criteria: \( F = 1.326, P = 0.2485 \) → no significant relationship. CI, confidence interval; SD, standard deviation.
was calculated for PT and DT (Table 4). Due to the number of individuals in the HD group, their reasons were classified into 10 categories (Table 5). These categories were determined by putting similar withdrawal reasons together in a logical system. For example, ‘current health status’ (category 1) grouped patients who, for various health reasons, both physical and mental, withdrew from PT. Categories were also determined by phrases that repeatedly came up within the case records in relation to patient withdrawal. For example, ‘prefer not to know’ (category 4) was one such phrase recorded in the case records of patients who withdrew from PT. The placing of patients into such categories was discussed with the case managing social workers, who would then agree or disagree to the placement of their particular patient into one of the categories. The distribution of these withdrawal reasons was fairly even, with the major reason being ‘not the right time for them’ (category 7) and unidentifiable using the techniques employed in this study (category 9). There were no statistically significant differences in the proportion of patients and category of withdrawal reason. Mean and median ages of individuals for each reason were calculated, and a comparison between male and female distribution for each reason was also performed (Table 5).

There was no statistically significant difference between males and females withdrawing from PT for HD. The stage of the PT process at which individuals withdrew was also recorded, with 49 (80.32%) during counselling and 12 (19.57%) at pre-results; 36 (59.01%) were female and 25 (40.98%) were male. Analysis of variance on withdrawal reasons did not reveal statistical significance.

The PT withdrawal individuals of the other neurodegenerative disorders group comprised entirely of SCA Figure 3

(A) Mean age of individuals with different CAG repeat lengths at predictive testing and neurological diagnosis of Huntington disease using the Unified Huntington Disease Rating Scale (UHDRS) criteria. (B) Mean interval in years from predictive testing until clinical diagnosis of Huntington disease using the UHDRS criteria compared with different CAG repeat lengths. Error bars show standard error of mean: ■ Mean age at predictive testing; ■ mean age at diagnosis.

Table 4 Population withdrawing from predictive and diagnostic gene testing for HD and other NDD

<table>
<thead>
<tr>
<th>Withdrawn groups</th>
<th>n</th>
<th>Total population</th>
<th>% of total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD PT</td>
<td>61</td>
<td>466</td>
<td>13.09</td>
</tr>
<tr>
<td>HD DT</td>
<td>2</td>
<td>132</td>
<td>1.29</td>
</tr>
<tr>
<td>NDD</td>
<td>4</td>
<td>52</td>
<td>7.69</td>
</tr>
</tbody>
</table>

χ² = 0.7989; degree of freedom = 1; two sided P = 0.3714 → not significant, that is, no statistically significant difference in the chance of withdrawal between the patients in the Huntington disease group or the other NDD. DT, diagnostic testing; HD, Huntington disease; NDD, neurodegenerative disorders (spinocerebellar ataxia, familial Creutzfeldt–Jakob disease and familial Alzheimer disease); PT, predictive testing.

Table 5 Reasons, age (years) and sex of patients withdrawing from predictive testing (PT) for Huntington disease

<table>
<thead>
<tr>
<th>Reason Category</th>
<th>Reason</th>
<th>n</th>
<th>No. male (%)</th>
<th>No. female (%)</th>
<th>Median age</th>
<th>Mean age ± 1 SD</th>
<th>95% CI for mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Current health status</td>
<td>6</td>
<td>1 (16.66)</td>
<td>5 (83.33)</td>
<td>46.1</td>
<td>48.2 ± 21.3</td>
<td>25.8–70.6</td>
</tr>
<tr>
<td>2</td>
<td>They/family are unable to cope</td>
<td>6</td>
<td>2 (33.33)</td>
<td>4 (66.66)</td>
<td>51.2</td>
<td>51.5 ± 13.4</td>
<td>50.0–52.9</td>
</tr>
<tr>
<td>3</td>
<td>with positive result</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Parent gene negative result</td>
<td>4</td>
<td>1 (25.00)</td>
<td>3 (75.00)</td>
<td>55.6</td>
<td>50.4 ± 19.2</td>
<td>19.9–80.9</td>
</tr>
<tr>
<td>5</td>
<td>Prefer not to know</td>
<td>5</td>
<td>3 (60.00)</td>
<td>2 (40.00)</td>
<td>36.6</td>
<td>43.5 ± 15.4</td>
<td>24.4–62.6</td>
</tr>
<tr>
<td>6</td>
<td>Ambivalent</td>
<td>6</td>
<td>4 (66.66)</td>
<td>2 (33.33)</td>
<td>43.1</td>
<td>43.8 ± 5.5</td>
<td>38.0–49.6</td>
</tr>
<tr>
<td>7</td>
<td>Relationship issues</td>
<td>4</td>
<td>2 (50.00)</td>
<td>2 (50.00)</td>
<td>34.1</td>
<td>34.4 ± 12.8</td>
<td>14.0–54.8</td>
</tr>
<tr>
<td>8</td>
<td>Not right time for them</td>
<td>10</td>
<td>4 (40.00)</td>
<td>6 (60.00)</td>
<td>31.6</td>
<td>35.7 ± 9.6</td>
<td>28.4–42.6</td>
</tr>
<tr>
<td>9</td>
<td>Unable to deal with PT process</td>
<td>3</td>
<td>0 (0.00)</td>
<td>3 (100.00)</td>
<td>37.1</td>
<td>37.8 ± 5.5</td>
<td>24.1–51.5</td>
</tr>
<tr>
<td>10</td>
<td>Unknown</td>
<td>10</td>
<td>6 (60.00)</td>
<td>4 (40.00)</td>
<td>45.5</td>
<td>47.2 ± 10.9</td>
<td>39.4–54.9</td>
</tr>
<tr>
<td>11</td>
<td>Other</td>
<td>5</td>
<td>2 (40.00)</td>
<td>3 (60.00)</td>
<td>43.7</td>
<td>49.3 ± 11.0</td>
<td>35.6–62.9</td>
</tr>
</tbody>
</table>

χ² = 0; degrees if freedom = 1; P = 1.0 → no statistically significant difference in the reasons patients withdraw from predictive testing with respect to age and sex. Reason code 10 (other) is for withdrawal reasons that do not fit into another category. These reasons are weakness of family history, individual died in a road traffic accident, individual lived in Alice Springs, and two withdrew for fear of discrimination by insurance companies. CI, confidence intervals; SD, standard deviation.
patients: two were SCA2, one SCA6 and one of an unknown SCA type. Fifty per cent were male and 50% were female. The mean age was 41.7 years. The withdrawal reasons given were ambivalence, current health status, unknown and withdrawal from the programme recommended by a physician on account of poor mental health with extensive drug and alcohol abuse. These withdrawals occurred at the counselling stages of PT. A $2 \times 2$ contingency analysis was performed on the different PT groups, and chi-square testing. No statistically significant difference was found between HD and non-HD in terms of withdrawal ($P = 0.3714$).

There was no recorded or other evidence of any individual committing suicide, self-harm, requiring urgent admission to a psychiatric hospital or being urgently referred for psychiatric assessment while participating in the PT programme, after neurological and psychiatric follow up for many years, surveillance by social workers, and liaison with the Neuroscience Unit and Huntington Association of Western Australia – the local community organisation whom we work closely with and who also monitor patients in the community.

### Reproductive genetic testing in HD

A total of 38 individuals was involved in reproductive genetic testing in HD: 34 in prenatal testing and four in PGD. Of the prenatal testing group, 12 (31.57%) were given an HD gene negative result, 11 (28.94%) an HD gene positive result and consequently terminated the pregnancy, 3 (7.89%) an HD gene positive result and continued with the pregnancy, and 8 (21.05%) withdrew from the prenatal testing process (Table 6). A summary of this data is represented in Figure 4.

The group who withdrew from prenatal testing comprised five (62.50%) patients where the female was at risk of HD and 3 (37.50%) patients where the male was at risk (Table 7). All withdrawals from prenatal testing occurred during the first trimester of pregnancy. The reasons for withdrawal from the prenatal process were as follows: one person decided that as HD was an adult-onset disease, a gene positive child could still lead a ‘good life’ beforehand; in another, it was the partner who terminated for other reasons; and one decided against knowing the gene status. Two people decided that they were unwilling to terminate a gene positive pregnancy, and in three patients the reason for withdrawal was unknown as they did not attend follow-up appointments despite confirmation and multiple attempts to do so. The withdrawals from prenatal testing mostly occurred at the counselling stages of PT.

Of the four individuals who went through PGD, none resulted in successful pregnancies after embryo insertion.

### Discussion

To our knowledge, this is the first study of its kind in Western Australia and is similar to studies performed in Victoria. Out of a total of 740 individuals at risk for HD and other neurodegenerative disorders, 132 (17.84%) underwent DT and 518 (70.00%) applied for the PT process, with 453 (61.21%) completing this process. Due to the majority of these patients being at risk of HD, the discussion shall focus on worldwide comparisons of PT in HD. The current at risk of HD population is unknown in Western Australia, and so a comparison of the above figures to world literature is not possible. Current worldwide literature suggests that up to 75% of at-risk individuals do not undergo PT. For example, in Europe, less than 20% undergo PT. Of the 65 individuals who withdrew from PT, the overwhelming majority (93.85%) were individuals at risk of HD who withdrew. This accounted for 12% of the total population applying for PT. The majority of individuals going through PT for HD are female. This was reflected at each stage of statistical analysis. A female majority has already been shown to be a common occurrence worldwide. The number of over 60-year-olds applying for HD PT was 23.33%, which is similar to observations elsewhere, such as 30% in the UK.

---

**Table 6** Reproductive genetic testing for Huntington disease: outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawn</td>
<td>8</td>
<td>21.05</td>
</tr>
<tr>
<td>Gene negative</td>
<td>12</td>
<td>31.57</td>
</tr>
<tr>
<td>Gene positive terminated</td>
<td>11</td>
<td>28.94</td>
</tr>
<tr>
<td>Gene positive continued</td>
<td>3</td>
<td>7.89</td>
</tr>
<tr>
<td>Pre-implantation genetic diagnosis</td>
<td>4</td>
<td>10.52</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4** Summary of reproductive genetic testing in Huntington disease. Gene results provided; withdrawn; pre-implantation genetic diagnosis.
Of the data concerning reproductive decision-making, the most interesting findings were of three individuals proceeding through prenatal testing and continuing with a gene positive pregnancy. On looking at the reasoning behind these decisions, it was found that one individual was originally ambivalent about having prenatal testing, and so perhaps should not have been offered the test. Another person changed her mind about termination after seeing the ultrasound scan of her baby, and consequently could not go through with a termination. This raises the question of whether ultrasound scans should be performed before the results of genetic testing. One patient had another gene positive pregnancy, which she aborted. Her reasoning behind continuing the first gene positive pregnancy was that by the time the genetic testing results came back, the foetus felt ‘too real and like a baby’ and so she could not terminate. However, it was also thought, from clinical observation and with the gift of hindsight, that at the onset of this pregnancy, she was beginning to show evidence of cognitive decline as a result of HD, and perhaps her impaired cognition influenced her decision-making. However, there are of course many other reasons why this woman may have decided not to terminate the pregnancy, which may not have been apparent to those involved in her case at the time. Ethical complexities arise when the at-risk parental status is unknown, as a gene positive result in the foetus would elucidate the presence of the mutation in the parent – such a situation might occur in minors where, for legal reasons, PT cannot be performed. There has been much research into the decision-making process of individuals choosing PT. Studies have looked at both individual PT and reproductive PT, and have also focused on the consequences of PT. However, a common theme is that the majority of individuals undergoing PT do so to relieve uncertainty regarding their gene status and so they will be able to plan for the future better.1 This was certainly confirmed when analysing the patients in this study – a common theme was ‘the burden of uncertainty’: individuals could no longer cope and so came forward for gene testing.

As the major withdrawal reasons ‘not the right time for them’ (category 7) and unknown (category 9), the themes around these patients shall be discussed. For category 7 patients, the majority of individuals said that they were not ready to go through PT as they needed more time to think over the implications and potential consequences of PT. One patient wanted to focus on her studies before completing PT and one patient’s marriage ended – it was too stressful to continue. The category 9 patients were individuals who did not attend subsequent appointments despite confirmation of appointments, on more than one occasion, and offered no reason; all of these patients were discussed with the social workers/case managers and they also had no knowledge as to why these individuals withdrew. On analysing this group of individuals, it was found that they ranged in age from 39 to 73 years old, with 45% being female and 56% being male. Eighty-two withdrew during the counselling stages, and 18% withdrew at the pre-results stage. Of the individuals who withdrew, none was directly related, apart from two who were sisters.

### Conclusion

This study has reported a 20-year experience of gene testing in HD and other neurodegenerative disorders. We have shown that PT is low risk in our centre, and there were small numbers of patient withdrawals. Some studies have identified anxiety and depression in asymptomatic carriers following gene testing;13 however, catastrophic reactions, such as suicide, seem not to occur more frequently after PT than in the general population using international protocols.16–19 Psychological distress after PT might relate to ego strength and motivation.17 Relationship with partners might suffer after PT.20 Low perceived social support, expectation of an unfavourable genetic test result before the testing procedure and being childless might predict an adverse outcome – individuals with limited social networks, expectations related to the gene test result and careful consideration of mental health prior to PT might help identify individuals at risk of PT and might require special attention.21

### Table 7

<table>
<thead>
<tr>
<th>Sex of individual at risk of HD</th>
<th>Trimester of pregnancy</th>
<th>Stage of withdrawal</th>
<th>Withdrawal reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1st</td>
<td>Counselling</td>
<td>HD is an adult-onset of disease</td>
</tr>
<tr>
<td>Female</td>
<td>1st</td>
<td>Counselling</td>
<td>Unwilling to terminate a gene positive pregnancy</td>
</tr>
<tr>
<td>Female</td>
<td>1st</td>
<td>Counselling</td>
<td>Unwilling to terminate a gene positive pregnancy</td>
</tr>
<tr>
<td>Female</td>
<td>1st</td>
<td>Pre-results</td>
<td>Unknown</td>
</tr>
<tr>
<td>Male</td>
<td>1st</td>
<td>Counselling</td>
<td>Decided against testing the foetus</td>
</tr>
<tr>
<td>Male</td>
<td>1st</td>
<td>Counselling</td>
<td>Partner terminated for other reasons</td>
</tr>
<tr>
<td>Male</td>
<td>1st</td>
<td>Counselling</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
guidelines are useful; however, in certain situations, the protocol might need to be modified for the specific requirements of a particular patient to minimise psychological stress, and as such the protocol might need to be prolonged or abbreviated depending on the circumstances.22

The observations in our study highlight the importance of adherence to internationally recognised guidelines for PT and the role of the multidisciplinary team in patient selection and risk minimisation.

**Acknowledgement**

The authors thank the staff at the Neurosciences Unit for their cooperation.

**References**

Total length of stay, costs and outcomes at final discharge for admitted patients with hip fracture: linked episode data for Australian veterans and war widows

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Key words
hip fracture, record linkage, length of stay, hospital cost, outcome assessment.

Abstract

Background and Aim: To identify the total duration of hospital stay, total hospital costs and outcomes at final discharge for a series of Australian patients with hip fracture.

Methods: The study type was retrospective cohort study using episode linkage within and between administrative databases. Study population is 2552 Australian veterans and war widows with primary diagnosis of hip fracture (International Classification of Diseases 10th revision, S72.0–S72.2) and hospital separation dates between 1 July 2008 and 30 June 2009. The unique identifying number within Department of Veterans’ Affairs health service databases was used to link records for relevant hospital episodes as defined. Additional linkages were made with data for residential care admissions and date of death.

Results: Mean length of stay (LOS) for unlinked acute episodes was 11.1 days, and cost of hospitalisation was A$13 095. Fifty-one per cent of these episodes ended with transfer to ongoing hospital care, 9.5% were discharged to residential aged care (RAC), in-hospital mortality was 6.5%, and 23% were discharged to ‘usual residence’. When data for all continuous episodes following hip fracture were combined, mean LOS was 30.8 days, costs were A$26 023 and in-hospital mortality was 11.1%. Additional linkage with RAC records identified 38% of final discharges to RAC facilities with 44% of patients returning to independent living.

Conclusion: For complex conditions such as hip fracture, a process of patient-specific episode linkage is required to identify accurately hospital LOS, costs and patient outcomes.

Introduction

The hospital management of hip fracture is a complex process for patients with complex clinical issues.1 Multiple episodes of hospital care are the norm rather than the exception to address care needs between initial admission and eventual discharge.1–3

Reports of hospital performance in respect of hip fracture that do not include information from all relevant hospital episodes provide an incomplete picture in respect of hospital resources and patient outcomes. The 2010 report on hip fracture by the Australian Institute of Health and Welfare (AIHW) noted that it could not track individual patients through the ‘hospital system’, and therefore, true outcomes could not be described.1 The most recent Australian study that identifies length of stay (LOS) and hospital mortality for hip fracture patients describes only the acute episode of care.1

Western Australia was the first Australian jurisdiction to practise systematic linkage of health databases6,7 but to date has not reported data for patient-based linked episodes with respect to hip fracture. The true values for LOS, cost and outcomes of treatment for hip fracture in Australian hospitals remain unknown.4 Wide disparities in international reports of hospital performance in respect of hip fracture arise mostly from differing capacity to link the relevant episodes in the hospital care process. Systems that provide patient-linked reporting include the Stockholm County Patient Care Register8 and the Hospital Episodes Statistics (HES) database for the English National Health Service (NHS).9 While reporting total LOS of 17 and 23 days, respectively, both reports ascribe less than half of the total hospital days to acute (surgical) episodes. Systems that report only acute episode data show median values of 5–9 days,5,10 while systems that...
incorporate rehabilitation have mean LOS of up to 44 days.\textsuperscript{10,11} There are commensurate differences in hospital outcome profiles.\textsuperscript{5,11–13}

This study will demonstrate, for a large cohort of elderly Australian patients, the very wide differences in LOS, hospital costs and patient outcome profiles between values derived through linkage of all relevant hospital episodes and those based upon unlinked data.

\section*{Methods}

The study population was drawn from veterans, war widows and other beneficiaries of Department of Veterans’ Affairs (DVA)-funded health services. In the study year, this comprised 185,985 persons (87,678 males, 98,317 females) aged 75 years or over, being 14\% of this Australian demographic at that time.

Study data were drawn from (DVA) databases for episodes of admitted care in public and private hospitals. All hospital separations between 1 July 2008 and 30 June 2009 with principal diagnosis of hip fracture (International Classification of Diseases 10th revision codes S72.0–S72.2) were identified. The following variables were extracted: the DVA-generated unique identifying number (UIN), age, sex, state and postcode, principal and secondary diagnoses, surgical procedure(s), LOS, admission and separation dates, costs and separation codes. A patient’s first recorded hip fracture during the study period was classified as the index episode.

Episode linkage is enabled through the UIN, a numeric that is assigned to every DVA client and attachable to all entries in all DVA databases. Patient transfers both within and between hospitals can thereby be tracked and linked from first admission to definitive discharge.

An additional DVA dataset describing dates of admission to and discharge from Residential Aged Care (RAC) was also linked to the hospital data through the UIN.

Costs for hospital episodes were transcribed directly from the DVA datasets. For public hospitals, these costs were calculated in accord with the National Hospital Cost Data Collection.\textsuperscript{14} For private hospitals, the cost was the sum of itemised services or contracted package costs according to standard DVA schedules.

Four different datasets were created:

1. Unlinked episodes with primary diagnosis code for hip fracture.
2. Patient-linked episodes with primary diagnosis of hip fracture. Linkage was created between episodes with matching UIN plus hip fracture diagnosis and interval of ≤1 day between separation date and next admission date.
3. All episodes subsequent to and continuous with the index episode. Criteria for linkage were: (i) Interval of ≤1 day between separation date and next admission date; the principal diagnosis for second and subsequent episodes was not censored. (ii) Separation code from preceding episode identified transfer to another hospital and interval to the subsequent recorded episode ≤7 days.
4. As for dataset 3 with additional linkage to the DVA database for RAC. If admission date to an RAC facility was ≤1 day different from that of final hospital discharge, then the separation code for transfer to RAC was recorded.

\section*{Exclusions}

Apparent second or subsequent fractures for the same patient within the study year, as identified by time lapse of more than 1 week between previous definitive discharge and next admission coded to hip fracture, were excluded.

\section*{Statistical analyses}

Student’s two-sample $t$-tests and Pearson’s Chi-squared tests were conducted when comparing groups for continuous and categorical outcomes respectively. Associations between patient age, LOS and costs were examined by linear regression. For comparison between datasets, linear and logistic mixed models were used, respectively, for continuous and binary outcomes, as data are paired according to patient.\textsuperscript{15} All calculations were computed in Excel 2003 (Microsoft Corporation, Redmond, WA, USA) or SAS9.2 (SAS Institute Inc., Cary, NC, USA).

\section*{Ethics}

Approval was granted by the DVA Human Research Ethics Committee in December 2010.

\section*{Results}

A total of 3177 episodes coded to hip fracture was identified, representing 2552 patients. An additional 94 episodes from 45 of these patients were identified as apparent second fractures. Females comprised 62.4\% of patients, with mean age of 86.6 years (range 59–100). Mean age for males was also 86.6 years (range 54–104).

\section*{LOS and costs}

Data for three levels of episode linkage are summarised in Table 1 and Table 2. For unlinked data (dataset 1), there...
was no significant difference between mean LOS for females and males ($P = 0.14$). Males and females also had similar values for episode costs ($P = 0.35$) LOS increased moderately with increasing patient age for females ($P = 0.25$) but not for males ($P = 0.4$).

The data of dataset 2 describe the acute phase of hospital management for hip fracture in which 85.6% of patients were treated surgically.

The linked data for episodes coded to hip fracture (dataset 2) found that of the 2552 patients, 1997 had a single episode coded to hip fracture, and 555 (21.7%) shared an additional 1180 episodes, with eight patients having four linked episodes coded to hip fracture. The episode : patient ratio was 1.25 for females and 1.24 for males ($P = 0.93$). Again, mean values for females and males did not significantly differ in respect of LOS ($P = 0.06$) or cost ($P = 0.22$). The mean LOS value for all patients was 2.3 days greater than for unlinked episodes (95% confidence interval (CI) 0.8–3.9, $P < 0.0001$), and the mean cost was higher by A$1804 (95% CI A$1372–2236, $P < 0.0001$).

The complete linkage process (dataset 3) identified 5228 individual episodes for 2552 patients of whom 1514 (59.3%) shared 4190 episodes, 2051 being for principal diagnoses other than hip fracture. The mean episode : patient ratio was 2.05 in this dataset. The most complex hospitalisations involved up to eight continuous episodes in up to five different hospitals.

There were 1172 patients (45.9%) referred for rehabilitation for a total of 1307 episodes. The average total time in admitted care for rehabilitation was 24.8 (95% CI 24.0–25.7) days per referred patient.

The complete process of episode linkage for the 2552 patients in this study identified a very wide range of values (range 1–310 days) for LOS about the mean of 30.8 days. One hundred and seventy-five patients had a hospital stay of 10 weeks or more. Total hospital costs ranged from A$680 to A$194 282 about the mean of A$26 023; 190 patients accrued more than A$50 000 of hospital costs (Table 2).

The key results for LOS and costs are summarised in Table 3.

### Hospital outcomes

The distributions of coded outcomes for all levels of linkage are shown in Table 4. For unlinked episodes, more than half of the episodes were ‘incomplete’, being transferred for further hospital care either in another hospital (43.5%) or in another unit within the same hospital (7.4%). The linkage of episodes coded to hip fracture (dataset 2) significantly reduced the reported rate of interhospital transfers from 53% to 35% ($P < 0.001$). The increase in identified rate of transfer to Aged Care was also significant ($P = 0.02$) as was the increased in-hospital mortality rate ($P = 0.04$).

The differences between reported values for patient outcomes in dataset 2 and dataset 3 were all highly significant ($P < 0.0001$). Essentially, when incomplete episodes were followed to their eventual discharge,
transfers for further care were superseded by codes for discharge to ‘usual residence’ or RAC. The linkage process also showed that in-hospital mortality rate for hip fracture was 72% higher than the rate identified in unlinked data.

Linkage with Aged Care databases showed that 701 patients (27.4%) had been RAC residents at the time hospital admission for hip fracture. Of these patients, 96.6% who survived hospital returned to residential care. For the other 1851 non-RAC patients in this study, 393 (21%) were found to have transferred to RAC, of which 14 were for short-term respite.

Discussion

Patient-based episode linkage has revealed that for this population of hip fracture patients, the total hospital stay, total costs and short-term outcomes all differed widely from values based upon unlinked episodes. There are ample Australian data describing both acute phase care14,15 for hip fracture and related rehabilitation episodes.17 The process of transfer between these two elements has also been well described.18 However, patient-identified data for both elements have not previously been linked for a substantial, national sample in this country.

Table 3 Summary of length of stay and hospital costs for linked and unlinked datasets

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Females (95% CI)</th>
<th>Males (95% CI)</th>
<th>All (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: Unlinked</td>
<td>10.9 (10.5–11.4)</td>
<td>11.4 (10.7–12.0)</td>
<td>11.1 (10.7–11.5)</td>
</tr>
<tr>
<td>3: All episodes S72.0–S72.2</td>
<td>30.9 (29.6–32.2)</td>
<td>30.5 (28.9–32.2)</td>
<td>30.8 (29.8–31.8)</td>
</tr>
<tr>
<td>Hospital costs (A$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: All episodes coded</td>
<td>14 797 (14 431–15 163)</td>
<td>15 068 (14 424–15 612)</td>
<td>14 899 (14 592–15 206)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

Table 4 Distribution of separation codes unlinked and linked data for patients with hip fracture 2008–2009

<table>
<thead>
<tr>
<th>Separation mode</th>
<th>Dataset 1 Unlinked</th>
<th>Dataset 2 Linked episodes hip fracture</th>
<th>Dataset 3 All continuous episodes</th>
<th>Dataset 4 Additional link to RAC data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>n = 1983</td>
<td>n = 1592</td>
<td>n = 1592</td>
<td>n = 1592</td>
</tr>
<tr>
<td>Transfer other hospital</td>
<td>46.2†</td>
<td>38.4</td>
<td>5.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Transfer within hospital</td>
<td>6.9</td>
<td>7.0</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Transfer to Aged Care</td>
<td>9.9</td>
<td>11.6</td>
<td>21.4</td>
<td>39.6</td>
</tr>
<tr>
<td>Death</td>
<td>4.3</td>
<td>5.3</td>
<td>7.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Home discharge</td>
<td>23.2</td>
<td>26.5</td>
<td>59.5</td>
<td>45.0</td>
</tr>
<tr>
<td>Other</td>
<td>9.5</td>
<td>11.2</td>
<td>4.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Males</td>
<td>n = 1184</td>
<td>n = 960</td>
<td>n = 960</td>
<td>n = 960</td>
</tr>
<tr>
<td>Transfer other hospital</td>
<td>39.2</td>
<td>29.6</td>
<td>4.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Transfer within hospital</td>
<td>8.2</td>
<td>8.4</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Transfer to Aged Care</td>
<td>8.8</td>
<td>10.5</td>
<td>17.8</td>
<td>34.8</td>
</tr>
<tr>
<td>Death</td>
<td>10.2</td>
<td>12.7</td>
<td>17.2</td>
<td>16.9</td>
</tr>
<tr>
<td>Home discharge</td>
<td>22.6</td>
<td>25.5</td>
<td>56.5</td>
<td>42.3</td>
</tr>
<tr>
<td>Other</td>
<td>11.0</td>
<td>13.3</td>
<td>4.3</td>
<td>3.7</td>
</tr>
<tr>
<td>All</td>
<td>n = 3177</td>
<td>n = 2552</td>
<td>n = 2552</td>
<td>n = 2552</td>
</tr>
<tr>
<td>Transfer other hospital</td>
<td>43.5</td>
<td>35.0</td>
<td>5.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Transfer within hospital</td>
<td>7.4</td>
<td>7.6</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Transfer to Aged Care</td>
<td>9.5</td>
<td>11.2</td>
<td>20.0</td>
<td>37.8</td>
</tr>
<tr>
<td>Death</td>
<td>6.5</td>
<td>8.1</td>
<td>11.2</td>
<td>11.1</td>
</tr>
<tr>
<td>Home discharge</td>
<td>23.0</td>
<td>26.1</td>
<td>58.4</td>
<td>44.0</td>
</tr>
<tr>
<td>Other</td>
<td>10.1</td>
<td>12.0</td>
<td>4.2</td>
<td>3.5</td>
</tr>
</tbody>
</table>

†All values are percentages of total separations. RAC, residential aged care.
While the creation of cross-linkages between institutional databases is now increasingly common, the additional process of this study – identifying and linking episodes of care for individual patients – is less frequently attempted in population-based reports. This study employs data drawn from DVA administrative databases. The primary function of these databases is for reconciliation of billing, and the patient identification is systematically matched within DVA against other departmental datasets. These features are in accord with the principles for minimising bias in studies using administrative databases.21

The presence of some coding inaccuracies within databases is endemic, but the rates of such errors are no longer seen as barriers to the valid use of databases for either human research or policy support.22 Recent reviews of Australian hospital databases have confirmed their comparatively very high levels of coding accuracy.23 The linkage with the RAC database in this study revealed that of the 701 patients admitted from RAC, 31 (4.4%) who returned to RAC had been assigned separation codes that specified other outcomes. An additional 316 patients were coded as separating to ‘usual residence’, which although correct was misleading without the added knowledge that they were already RAC residents. Among the 1851 non-RAC patients, 99 (5.3%) were shown to have transferred to RAC despite other separation codes having been assigned. The study population has demographic features typical of the DVA population. Males comprise 37.6% of the 2552 patients in this study, significantly higher than 27.4% (P = 0.004) of hip fracture episodes attributed to males in Australian data.4 Mean age of DVA patients with hip fracture in 2008–2009 was 86.6 years compared with 83 years for Australian females and 81 years for males in 2006–2007.1 Females aged 85 years or older accounted for 79% of DVA episodes compared with 62% of non-DVA episodes (P < 0.001). Equivalent values for males aged 85 years or over were 28% and 8% respectively.16 The absolute values reported by this study for LOS, costs and outcome rates must be interpreted in the context of these demographics.

However, it is the dimensions of the differences between results from unlinked and patient-linked data that this study primarily addresses. These differences would appear to be generally applicable, given the similarities between matchable data from this study and nationally reported datasets as described later.

For unlinked episodes in patients aged 75 years and over, LOS in this study – 10.9 days for females and 11.4 days for males – closely matched values derived for non-DVA patients (11.2 and 11.8 days respectively).16 Costs for unlinked episodes in this study (A$13 095) closely matched the mean cost of A$13 012 calculated from the AIHW data for 2006–2007.7 The mean duration of rehabilitation episodes in this study was 22.2 days, almost identical with the Australian benchmark for ‘orthopaedic fractures’ (22.6 days) in 2009.17 The average number of episodes per patient in dataset 2 was 1.25, while the equivalent ratio in a large series of hip fracture patients from New South Wales was 1.28 (L. Taylor, NSW Health Ministry, pers. comm., 2012). The lack of significant age or gender gradients in the DVA ratios suggest that any distortions arising from the DVA demographics would be minimal.

For dataset 3, no attempt was made to censor the principal diagnoses for episodes continuous with the index episode. The wide spectrum of clinical conditions – post-acute care, complications or comorbidities – contributes to a diversity of hospital care for hip fracture.1,3 The allowed interval of ≤7 days between an episode ending in transfer to another hospital and a subsequent episode reflects the uncommon occurrence of episodes not billed to DVA and thus not recorded in DVA databases.

The management of hip fracture frequently involves an emergency hospital admission in which diagnosis is established, with prompt transfer to another episode for definitive (usually surgical) treatment. In this study, 439 of 506 episodes (87%) with LOS ≤2 days and separation codes other than death were transferred to another hospital.

Comparative international reports of LOS for hip fracture vary widely. The Stockholm County Patient Care Register for 2007 identified mean LOS of 17.3 days comprising 7.0 days for acute phase care and 10.3 days for rehabilitation.8 Another Swedish study reported 11.3 days for acute phase care and 27.9 days for ‘total hospitalisation’ in 2003–2004.24 French data for 2005–2006 identified 16.2 days in acute phase care followed by 27.8 days in rehabilitation.11 HES for English NHS reports hospital ‘spells’ of linked episodes under different consultants. These data describe LOS of 23.0 days for hip fracture in 2008–2009, a value that appears to include inpatient rehabilitation, as such episodes are not separately reported in any numbers. Data for private hospitals were ‘mostly excluded’ from this report.8 A Japanese study reports LOS of 34 days and notes a marked contrast with the median of only 5 days reported from the United States. Hospital stay in Japan was inclusive of post-acute care, whereas the American data related purely to unlinked episodes of acute surgical treatment.10 Scottish data from 2006 reported a mean of 25 days for total LOS, linking orthopaedic, rehabilitation and ‘other’ episodes, but this calculation excluded ‘at least a quarter’ of patients who were still in hospital at 42 days.25
Recently reported in-hospital mortality rates are similarly diverse. In Australia, the national data presented by AHW for 2006–2007 report 6%,4 while a series from a Sydney teaching hospital shows 4.9% for 2003–2007.3 The French Hospital National Data identifies deaths for only 2.8% of patients aged 40+ years in 2008.11 These figures all relate to data that describe unlinked episodes for acute treatment. Hospital mortality reported in the English HES for the period 2006–2008 was 13.7% based on linked episodes.26

The differences in profiles of hospital separations between unlinked and episode-linked datasets are substantial. Overall in-hospital mortality in this study increased to 11.1% from 6.5% in unlinked data, and the very high proportion of interhospital transfers in unlinked data is almost entirely replaced by discharges to ‘home’ or RAC in fully linked results. The additional linkages with Aged Care data produced, in this elderly cohort, substantial revision of separation codes with transfers to Aged Care increasing from 20.0% to 37.8%.

In an elderly and medically complex patient cohort, extra days in hospital are associated with additional untoward outcomes. Quoted rates for hospital mortality and other outcomes for hip fracture may be more dependent upon the definition of ‘separation from hospital’ than upon standards of practice within a given hospital system.

Conclusion

A process of patient-based episode linkage to identify the total hospital stay and definitive outcomes in respect of hip fractures is presented. Two-thirds of the study population experienced transfer from acute phase episodes for ongoing admitted care, with 46% of all patients being referred for rehabilitation. Total LOS was 30.8 days, almost three times the value for unlinked data (11.1 days). Hospital costs were almost double the values identified in unlinked data. In-hospital mortality was shown to be higher by over 70%, and transfer to RAC was four times more frequent than the values obtained from conventional reports based on unlinked episodes.

References

Medicare and Veterans Affairs Hospitals. 


Hip fractures among Indigenous Western Australians from 1999 to 2009

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Key words
hip fracture, indigenous, osteoporosis, fall.

Abstract

Background: Minimal trauma hip fractures are prevalent in Australia. The incidence rate and trend of hip fractures in Indigenous Western Australians have not been formally reported.

Aims: To evaluate incidence rates and trend of minimal trauma hip fractures in Indigenous and other Western Australians aged 40 years and over in 1999–2009

Methods: Hip fracture data were obtained from an administrative database for all hospitalisations in Western Australia. Age-standardised incidence rates were calculated using direct standardisation, and standardised rate ratios were calculated using the indirect method. Trend in incidence rates were calculated using Poisson regression.

Results: In 1999–2009, 11,844 admissions for minimal trauma hip fractures were reported among Western Australians aged 40 years and over, of which 201 were recorded as indigenous. The age-standardised hip fracture rate was 273.0 (95% confidence interval (CI) 230.7–315.4) per 100,000 person-years for indigenous adults and 148.8 (95% CI 146.1–151.5) per 100,000 person-years for non-indigenous adults. The standardised morbidity ratio was 2.2 (95% CI 1.9–2.5). Over this period, age-standardised rates increased by an average of 7.2% per year among indigenous adults (P = 0.006), whereas non-indigenous rates fell by an average of 3.4% per year (P < 0.001). The relatively higher rates among indigenous adults were more evident in the younger age groups.

Conclusion: There is a widening gap in minimal trauma hip fracture rates between indigenous and other Western Australians. This study demonstrates a need for public health review and management strategies to reduce falls and hip fracture in the indigenous community.

Introduction

Minimal trauma hip fractures, also known as osteoporotic hip fractures, are prevalent in Australia and affect mainly older people aged 65 years and over.1 They are predictive of mortality and can cause significant functional impairment, pain and substantially reduced quality of life.1,2 Hip fractures impose a large economic burden to the society because of healthcare costs related to treatment and rehabilitation, as well as costs for community service provision and residential aged care facility beds.1 Although the estimated incidence rate of osteoporotic hip fracture in Australia is on the decline,4,3 it remains a significant health burden that is expected to increase with our ageing population and overall population growth.5

According to the latest population census, there are 548,369 indigenous people in Australia (2.5% of the total population).7 In 2008, a national healthcare agenda was developed with a focus to closing the gap of health and social inequalities between Indigenous and non-Indigenous Australians.6 It is well established that Indigenous Australians suffer from higher health risk and disease burden, and also have a lower life expectancy compared with other Australians.9 In particular, a preliminary report has indicated that they are more likely to be hospitalised for an osteoporotic hip fracture than other Australians, and at a much younger age than other Australians at the time of their fracture.1 Recognising this
existing health discrepancy and elucidating the underlying reason for this phenomenon is crucial to achieving our goal of reducing morbidity and mortality in this disadvantaged group of individuals.

In Western Australia (WA), there are 69,665 indigenous people, accounting for 3.1% of the total WA population. Hip fracture rates in this specific population have yet to be formally reported. In this study, we aimed to (i) obtain a robust estimate of the number of minimal trauma hip fractures that had resulted in hospitalisation in WA over a 10-year period; (ii) evaluate the incidence rate of minimal trauma hip fractures, taking into account the differences in population age structure in the indigenous population; and (iii) further delineate the trend in incidence rates between Indigenous and non-Indigenous Western Australians over the same period.

**Methods**

**Study design and population**

We conducted a descriptive epidemiological study utilising de-identified hospitalisation data between July 1999 and June 2009 from the WA Hospital Morbidity Data System (HMDS), an administrative database for all public and private hospital admissions in the state. Western Australians aged 40 years and over were included in this study. Data from the HMDS were coded in standardised International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification codes. For the purpose of this study, hip fractures were defined as fractures at the neck of the femur, pertrochanteric and subtrochanteric regions (codes S72.0, S72.1, S72.2), with external causes related to minimal trauma (codes W00, W01, W03-08, W18-19, W22, W50-51, W54.8).

Our study was exempted from formal ethical review by the Western Australian Aboriginal Health Information and Ethics Committee as all data had been de-identified, and this project represented quality improvement and surveillance.

**Separations**

Some patients might have had more than one episode of care because of interhospital transfers for acute care, rehabilitation and fracture complications. These transfers were excluded from analyses to avoid overestimation of the fracture rates and number. By assigning a unique patient identifier, we were able to define a separation as a new admission or interhospital transfer. An admission was classified as a transfer if it was coded as a transfer and the admission date was less than 24 h from the patient’s previous separation. When this was performed, we found additional 30 indigenous records incorrectly flagged as interhospital transfers. These separations were subsequently included in our study as incident cases of hip fracture. This method has been validated by comparison with the Trauma Registry subset maintained at Royal Perth Hospital.

**Statistical analysis**

Statistical analyses were performed using the Department of Health WA’s Rates Calculator as described elsewhere. Descriptive statistics were calculated for the demographic and hip fracture characteristics according to categories of indigenous versus non-indigenous adults. To obtain the crude hip fracture rate, the numerator was defined as the total number of admissions for minimal trauma hip fracture in indigenous and non-indigenous adults aged 40 years and older, respectively, over 10 years. The denominator was the estimated residential population for both groups aged 40 years and older, respectively, as reported in the 2006 population census. Age was then stratified into 5-year age groups, and age-standardised hip fracture rates were calculated using the direct standardisation method. Poisson regression was applied to examine trends of incidence rates over time. In order to improve reliability, all rates were calculated using 3-year rolling averages. The study population was further dichotomised by gender, and the direct method was used to calculate the age-standardised rates for males and females in both groups respectively. A subanalysis of age-standardised rates stratified by area of residence was also performed using the direct method. Standardised rate ratios (RR) were calculated using the indirect method. Rates were reported as per 100,000 person-years with 95% confidence interval (CI).

**Results**

Demographic and hip fracture characteristics of the study population are shown in Table 1. From July 1999 to June 2009, a total of 11,844 admissions for minimal trauma hip fractures was reported among Western Australians aged 40 years and above. Two hundred and one (1.7%) were of indigenous origin, among which just over half (54.2%) were female. 26.9% of the indigenous adults were 80 years old and over as compared with 67.4% of the non-indigenous adults. More than 80% of the indigenous people lived outside of WA metropolitan areas compared with 21.5% of the non-indigenous people. The most common fracture site was the pertrochanteric region for the indigenous adults and the neck of the
femur for the non-indigenous adults. Majority of the fractures were preceded by falls in both groups. Over the 10-year period, the crude hip fracture rates for both indigenous and non-indigenous adults were almost equal with a RR of 1.0. Using the direct method, the age-standardised hip fracture rate was 273.0 (95% CI 230.7–315.4) per 100 000 person-years for indigenous adults and 148.8 (95% CI 146.1–151.5) per 100 000 person-years for non-indigenous adults. Based on an indirect standardisation, the standardised morbidity ratio was 2.2 (95% CI 1.9–2.5). As shown in Figure 1, age-standardised rates increased by an average of 7.2% per year among indigenous adults ($P = 0.006$), whereas non-indigenous rates fell by an average of 3.4% per year ($P < 0.001$) over this period.

Figure 2 demonstrates the age-specific hip fracture rates in indigenous and non-indigenous males and females. The age-standardised rate for indigenous males was 244.6 (95% CI 187.3–302.0) per 100 000 person-years compared with 97.7 (95% CI 94.2–101.3) per 100 000 person-years for non-indigenous males. The age-standardised rate for indigenous females was 302.8 (95% CI 240.7–364.9) per 100 000 person-years compared with 183.6 (95% CI 179.7–187.4) per 100 000 person-years for non-indigenous females. Based on indirect standardisation, the risk of admission for hip fractures was 3.3 times higher among indigenous males (RR 3.3, 95% CI 2.7–4.1) and 1.8 times higher among indigenous females (RR 1.8, 95% CI 1.5–2.2) compared with their non-indigenous counterparts. The standardised RR between indigenous and non-indigenous males and females decreased across increasing age groups, with no apparent discrepancy from 80 years of age onwards (Table 2).

We performed a subanalysis of hip fracture rates stratified by area of residence. The age-standardised rate was 303.2 (95% CI 253.4–352.9) per 100 000 person-years for indigenous adults living in non-metropolitan areas and 175.0 (95% CI 168.1–181.9) per 100 000 person-years for non-indigenous adults living in these areas.

<table>
<thead>
<tr>
<th>Table 1 Demographic and hip fracture characteristics of Indigenous and non-Indigenous Western Australians aged 40 years and above, 1999–2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous</td>
</tr>
<tr>
<td>n = 201</td>
</tr>
<tr>
<td><strong>Age group (years), n (%)</strong></td>
</tr>
<tr>
<td>40–49</td>
</tr>
<tr>
<td>50–59</td>
</tr>
<tr>
<td>60–69</td>
</tr>
<tr>
<td>70–79</td>
</tr>
<tr>
<td>≥80</td>
</tr>
<tr>
<td><strong>Female gender, n (%)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Geographic area of residence, n (%)</strong></td>
</tr>
<tr>
<td>Perth Metropolitan</td>
</tr>
<tr>
<td>Non-metropolitan</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td><strong>Site of fracture, n (%)</strong></td>
</tr>
<tr>
<td>Neck of femur</td>
</tr>
<tr>
<td>Femoral trochanteric</td>
</tr>
<tr>
<td>Subtrochanteric</td>
</tr>
<tr>
<td><strong>Causes, n (%)</strong></td>
</tr>
<tr>
<td>Falls</td>
</tr>
<tr>
<td>Other causes (e.g. stuck or hit by another object, animal or person)</td>
</tr>
</tbody>
</table>

Numbers less than five have been suppressed for confidentiality purposes. †Does not include suppressed numbers.

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those living in WA metropolitan areas, the age-standardised rate was 222.7 (95% CI 125.6–319.9) per 100 000 person-years for indigenous adults and 141.7 (95% CI 138.8–144.7) per 100 000 person-years for non-indigenous adults.

Discussion

Our study has revealed a significantly disproportionate increase in minimal trauma hip fracture rates among Indigenous Western Australians aged 40 years and above between 1999 and 2009. This is in contrast to the declining incidence rates in their non-indigenous counterparts, highlighting the widening gap in this important adverse health outcome between the two groups over the 10-year period. Indigenous adults were twice as likely to be hospitalised for hip fractures compared with non-indigenous adults, and the relative risk was more pronounced for males than for females. The relatively higher hip fracture rates among Indigenous Western Australians were also more evident in the younger age groups, implicating a higher risk burden among younger indigenous adults and whom preventative and management strategies should hence be targeted at.

Our study complements and extends a previous nationwide analysis of osteoporotic hip fracture rates over a 2-year period between 2005 and 2007, using combined data for most Australian states, including WA. According to this report, the risk of having a hip fracture is twice as likely among Indigenous Australian males (RR 2.01, 95% CI 1.70–2.54) and 26% more likely in Indigenous Australian females (RR 1.26, 95% CI 1.07–1.47) compared with their non-indigenous counterparts.1 Our study results are concordant with these findings, suggesting a higher risk profile among indigenous males in WA than indigenous females and their non-indigenous counterparts. Macintosh et al. conducted a smaller institution-based study in the state of Queensland over a 3-year period between 1997 and 2000.13 Similar to our findings, indigenous males had higher age-adjusted hip fracture rates than non-indigenous males, albeit no difference in the fracture rates between indigenous and non-indigenous females in that study. The possibility of selection bias and reduced statistical power due to the smaller sample size should be considered during the interpretation of these findings.

Minimal trauma hip fractures are commonly caused by accidental falls, and their occurrences also underscore the presence of osteoporosis. Several clinical and lifestyle risk factors may contribute to lower peak bone mass and an increased propensity to fall in indigenous adults, including vitamin D insufficiency, diabetes, smoking, excessive alcohol consumption and physical inactivity.14,15 Some of these health risk factors are more common in indigenous

Table 2

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Age-specific rate ratio† (95% CI)</th>
<th>Standardised rate ratio† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40–49</td>
<td>50–59</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13.7 (6.0–22.9)</td>
<td>12.0 (7.1–17.5)</td>
</tr>
<tr>
<td>Female</td>
<td>3.2 (0.3–7.5)</td>
<td>4.8 (2.5–7.4)</td>
</tr>
</tbody>
</table>

†Using non-indigenous population as the reference group. CI, confidence interval.
males than females and may account for the higher disease burden and injuries at younger ages among this particular group. The observation that the risk ratios of hip fractures between indigenous and non-indigenous adults declined with increasing age may be partly explained by the premature mortality among younger indigenous people, resulting in relatively healthier survivors into the older indigenous age groups.

We observe that more than 80% of our indigenous cohort resided outside WA metropolitan areas, a proportion in excess of what might be expected from the total Indigenous Western Australians (60.4%) living in non-metropolitan areas. Relative underactivity of health services for the detection and management of osteoporosis has been reported in these regions, and the management rates by general medical practitioners for preventative measures among Indigenous Australians are also lower than other Australians. Our analysis of hip fracture rates stratified by area of residence suggests that only a small portion of the elevated fracture risk might be attributable to non-metropolitan status and that the majority of the risk is attributable to other factors associated with indigenous status. Nevertheless, as primary healthcare remains the mainstay of osteoporosis management, there is an ongoing need to review indigenous health policy and expenditure in order to deliver these services adequately.

The strengths of our study include the large population-based sample and the longitudinal assessment of age-standardised hip fracture rates over an extended 10-year period. The application of a unique person identifier to each individual enabled us to improve the identification of separations due to interhospital transfers and thus minimise misclassification of cases. The adoption of this methodology was validated and has been demonstrated to improve the accuracy of our data estimates. Limitations include the possibility of undercounting due to non-response during census data collection. The complexity of indigenous identification, which was based on self-report, can also affect the quality of census and hospital data. Indigenous population growth had been at twice the rate of the overall population since 1996, and in WA, there was an associated 18% increase between 2001 and 2006 as compared with the national average of 12.8% for the total indigenous population in the same period. Interpretation of hip fracture rates during this time will need to take this caveat into consideration. Our study population comprised mainly Western Australians, and thus the findings may not be generalised to the indigenous populations in other states or countries.

Conclusion

The age-standardised rate of minimal trauma hip fractures is increasing among the Indigenous Western Australians, in contrast to a declining rate among the non-Indigenous Western Australians. Our study highlights a pertinent health gap between the indigenous and non-indigenous Australians, and demonstrates the need for public health review and management strategies to reduce falls and hip fracture in this disadvantaged community.

Acknowledgements

The authors thank Ms Avonia Donnellan (Senior Policy Officer, Health Network Branch, Department of Health WA), Ms Karina Moore (Senior Development Officer, Health Network Branch, Department of Health WA) and Dr Hannah Seymour (Geriatrician, Royal Perth Hospital) for their assistance in this study.

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Impact of opening a new emergency department on healthcare service and patient outcomes: analyses based on linking ambulance, emergency and hospital databases

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Key words
emergency health services, data linkage, outcomes research, crowding.

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Abstract

Background: Emergency department (ED) crowding caused by access block is an increasing public health issue and has been associated with impaired healthcare delivery, negative patient outcomes and increased staff workload.

Aim: To investigate the impact of opening a new ED on patient and healthcare service outcomes.

Methods: A 24-month time series analysis was employed using deterministically linked data from the ambulance service and three ED and hospital admission databases in Queensland, Australia.

Results: Total volume of ED presentations increased 18%, while local population growth increased by 3%. Healthcare service and patient outcomes at the two pre-existing hospitals did not improve. These outcomes included ambulance offload time: (Hospital A PRE: 10 min, POST: 10 min, \(P < 0.001\); Hospital B PRE: 10 min, POST: 15 min, \(P < 0.001\)); ED length of stay: (Hospital A PRE: 242 min, POST: 246 min, \(P < 0.001\); Hospital B PRE: 182 min, POST: 210 min, \(P < 0.001\)); and access block: (Hospital A PRE: 41%, POST: 46%, \(P < 0.001\); Hospital B PRE: 23%, POST: 40%, \(P < 0.001\)).

Time series modelling indicated that the effect was worst at the hospital furthest away from the new ED.

Conclusions: An additional ED within the region saw an increase in the total volume of presentations at a rate far greater than local population growth, suggesting it either provided an unmet need or a shifting of activity from one sector to another. Future studies should examine patient decision making regarding reasons for presenting to a new or pre-existing ED. There is an inherent need to take a ‘whole of health service area’ approach to solve crowding issues.

Introduction

International,1,2 national1 and state4–6 organisations recognise that improvements in or expansions of healthcare related services are required to meet the healthcare needs of the community in a safe and sustainable fashion. A variety of interventions designed to improve the timeliness of care that target the input, throughput or output aspect of the patient journey has been described.5 One strategy aimed at alleviating the influx of patients into an overcrowded hospital system is to close the Emergency Department (ED) (i.e. shut it down altogether, or on a temporary basis to ambulance traffic).7,8 This strategy, on the whole, is suboptimal for patients as treatment delays and in some cases, death can result.7,8 Furthermore, when ambulance diversion occurs at one ED, it often causes crowding and subsequent diversion at nearby facilities.7,9 This has been referred to as the ‘network effect’.7

Other approaches directed towards alleviating pressures of increasing patient volumes and overcrowding are to open an additional ED or expand the size and number of beds in an existing ED. Little literature exists on the impact these measures make to service delivery and
patient outcomes. Literature available regarding opening new or expanded ED is mainly descriptive\textsuperscript{10–12} with some before and after measured outcomes\textsuperscript{10,13} and discussions on ‘lessons learnt’.\textsuperscript{11,12,14} Previous US studies that discuss opening new/expanding ED have mainly focussed on outcomes from acute care provision facilities (Level I and II trauma centres). The United States has different health funding systems and level of care provisions to those of Australia.

The purpose of this study was to examine the impact on patient and health service outcomes for surrounding hospitals and ambulance services in the 12 months before and after an additional ED was opened in South East Queensland, Australia by deterministically linking three databases: ambulance, ED and hospital admissions.

\section*{Methods}

\subsection*{Design}

Comparative and time series design was used to identify changes in patient, healthcare organisation and ambulance service outcomes by linking data from three major health service data systems that capture information related to a patient’s acute care journey including ambulance transport, and/or ED attendance and/or hospital admission.

Approval to conduct this study was obtained from the Human Research Ethics Committees of participating sites and ambulance service as well as Queensland Health’s Research Ethics and Governance Unit.

\subsection*{Sample and setting}

The study sample consisted of patient presentations made to three South East Queensland public teaching hospital ED between 3 September 2006 and 3 September 2008. A description of the study sites is presented in Table 1. The Queensland Ambulance Service (QAS) transported patients to these and other ED within the region. These three public hospitals, along with three private hospitals, served a total population of approximately 800 000.\textsuperscript{15}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
Characteristic & Hospital A & Hospital B & Hospital C \\
\hline
Hospital type & Tertiary, public, teaching & Urban, public, teaching & Urban, public, teaching \\
Distance from new ED (km) & 15 & 58 & 0 \\
No. hospital beds & 473 & 290 & 200 \\
No. ED beds: & & & \\
Acute care & 31 & 22 & 25 \\
Observation ward & 10 & 10 & 12 \\
Fast track & 4 & 4 & 4 \\
\hline
\end{tabular}
\caption{Study sites summary}
\end{table}

\textsuperscript{ED, emergency department.}

\textsuperscript{Crilly et al. © 2013 The Authors Internal Medicine Journal © 2013 Royal Australasian College of Physicians}

\subsection*{Data collection}

Data obtained were based on a previous conceptual framework of ED crowding,\textsuperscript{16} predictors associated with crowding, ambulance diversion and in-hospital mortality literature. The use of databases for research is a popular method for examining the distribution and determinants of health-related states or events in specified populations.\textsuperscript{17} The Decision Support Service unit of each hospital and the QAS provided the routinely collected data from the following health information systems: Emergency Department Information System (EDIS), Hospital Based Corporate Information System (HBCIS) and electronic Ambulance Report Form (eARF). EDIS is the software used within most Australian public ED. It records and stores information on each patient’s ED episode. HBCIS is the inpatient administration system used within Queensland public hospitals. It contains patient demographic information as well as information regarding each patient’s hospital admission episode. The eARF is the QAS record of information on each patient’s ambulance episode. Data collected from each health information system for this study is presented in Table 2.

The Australasian Triage Scale (ATS) is a tool used as an indicator of clinical urgency.\textsuperscript{18} It is measured on a scale of 1 to 5, where 1 is the most urgent. ED length of stay (LOS) was calculated from ED arrival and departure time.\textsuperscript{18} Ambulance offload time >15 min\textsuperscript{19} and >30 min was calculated from the QAS data from arrival at ED and stretcher offload time. Access block was calculated for patients requiring hospital admission where ED LOS was 8 or more hours.\textsuperscript{20}

We used Health Data Integration (HDI), an automated deterministic linking approach developed by the Commonwealth Scientific and Industrial Research Organisation (CSIRO) to link data from the three separate health information system databases (QAS, EDIS and HBCIS). The HDI linking strategy has previously been tested on this type of data for accuracy with high sensitivity, specificity and positive predictive value (PPV) yields.\textsuperscript{21}
Statistical analysis

Descriptive statistics were used to describe the profile of all patients presenting to three EDs within South East Queensland. These statistics included median and interquartile range for age and time variables and frequency distributions for categorical variables. Inferential statistics were used to identify differences between groups. Groups were viewed as independent from each other. Mann–Whitney U tests (for continuous data with skewed distribution) and Chi-squared tests (for categorical variables) were used to test differences between groups. Using daily time points (i.e. 365 pre- and post-time points), time series analysis (using Autoregressive Integrated Moving Average (ARIMA) modelling) was performed for site A and B to test for any significant change in three outcome measures: the percentage of presentations for ambulance offload time >30 min, ED LOS and per cent of access block following the opening of the new ED. Data management and statistical analyses were conducted using SPSS software, version 17 (SPSS Inc, Chicago, IL, USA) and R. Significance for all results was defined as $P < 0.05$.

Results

The data inclusion flow diagram is presented in Figure 1. Total ED attendances in the district increased 18.4% during the study period. A combined total of 119,459 patient presentations was made to the EDs of Hospital A and B in the 12 months following Hospital C’s ED opening, and 35,287 patient presentations were made to the new ED (Hospital C) during its first 12 months. While the total number of ED presentations increased with the addition of the new ED, attendances decreased at the EDs of Hospital A and B. Demographic characteristics for patient presentations made to each site are presented in Table 3. Age and sex differences did not vary greatly at each site from one year to the next; the median age was around 30 years and males represented between 50% and 53%.

ED characteristics for patient presentations made to each site are presented in Table 4. For Hospital A and B, when the year prior to the new ED opening was compared to the year post, significant differences for the characteristics mode of arrival, triage category and season were identified. For Hospital A, lower proportions of ambulance arrivals, ATS 3 presentations, as well as autumn presentations occurred in the 12 months following the new ED opening. For Hospital B, lower proportions of ambulance arrivals, ATS 4 and ATS 5 presentations, as well as autumn and winter presentations occurred in the 12 months following the new ED opening. The majority of ED characteristics for patient presentations made to Hospital C (with the new ED) closely reflect the other sites (during post year). However, there were lower proportions of ambulance and police arrivals, ATS 1 and ATS 3 presentations and higher proportions of walk-in and ATS 5 presentations.

Ambulance, ED and hospital admission outcomes are presented in Table 5. For both Hospital A and B, significant differences for all QAS outcomes (except offload time >30 min in Hospital A), all ED outcomes and all hospital admission outcomes (except for Hospital LOS in Hospital A) were identified when PRE versus POST time frames were compared. For both Hospital A and B, higher proportions of all aforementioned outcomes were noted, except for in-hospital mortality which decreased from PRE to POST (Hospital A: pre 3.0% vs post 2.2%, $P < 0.001$; Hospital B: pre 2.7% vs post 1.9%, $P < 0.001$).

Time series analysis (using ARIMA modelling) was performed to evaluate the opening of the new ED on three outcomes: offload time >30 min (Fig. 2), ED LOS (Fig. 3) and access block (Fig. 4). After accounting for the cyclic, seasonal and long-term trend changes, we tested if the opening of the new ED had a significant effect on the series. Table 6 presents summary data from these models. There was a significant increase in access block at Hospital A and no significant impact on offload time or ED
Ambulance offloads at ED (3 September 2006 – 2 September 2008)

286 037 presentations to ED (3 September 2006 – 2 September 2008)

73 304 admissions to hospital via ED (3 September 2006 – 2 September 2008)

LINK 1 (EDIS to QAS)

81 057 QAS presentations linked with 286 037 ED presentations

70 464 admissions linked with the 286 037 ED presentations and 81 057 QAS presentations

- Exclusions from linked data set
  - EDIS duplicate records
  - Incorrect age (>104)
  - Incorrect sex (3, 9)
  - ED LOS (negative)
  - EDIS-HBCIS duplicate records

285 463 ED presentations, 67 941 admissions and 8014 QAS arrivals linked, clean and analysable

Figure 1 Data inclusion flow diagram: ambulance service and three hospitals; 2-year study period. ED, emergency department; EDIS, Emergency Department Information System; HBCIS, Hospital Based Corporate Information System; QAS, Queensland Ambulance Service; LOS, length of stay.
LOS. All indicators were significantly increased in Hospital B (furthest from the new ED) after the new ED opened.

Discussion

Growth

This study was set within the context of an increasing acuity and patient presentations to EDs with a fixed number of hospital beds and limited number of ambulance resources. The total volume of ED presentations increased 18% within the region, despite local population growth of only 3.1%. This increase in ED presentations is higher than the 11.5% growth in presentations following the opening of a new ED in the United States in 2004 and higher than the annual increase of ED attendances within Australian and Queensland public ED; 5.1% and 6.4%, respectively from 2006/2007 to 2007/2008.

Contemporary conceptions of overcrowding suggest that overcrowding in the ED reflects broader hospital issues and inefficiencies in bed and resource

Table 3 Demographic characteristics of emergency department (ED) patient presentations, by site and year

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hospital A</th>
<th>Hospital B</th>
<th>Hospital C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>P-value</td>
</tr>
<tr>
<td>Median age (IQR [years])</td>
<td>32 (19–54)</td>
<td>31 (19–52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36.66% (53.1%)</td>
<td>32.44% (53.1%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32.44% (46.9%)</td>
<td>28.68% (46.9%)</td>
<td></td>
</tr>
</tbody>
</table>

IQR, interquartile range.

Table 4 Emergency department characteristics of patient presentations, by site and year

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hospital A</th>
<th>Hospital B</th>
<th>Hospital C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>P-value</td>
</tr>
<tr>
<td>Mode of arrival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walked in</td>
<td>44.01% (64.3%)</td>
<td>40.56% (66.4%)</td>
<td></td>
</tr>
<tr>
<td>Ambulance</td>
<td>24.01% (34.7%)</td>
<td>19.67% (32.2%)</td>
<td></td>
</tr>
<tr>
<td>Police</td>
<td>6.46% (0.9%)</td>
<td>8.15% (1.3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4.70% (0.1%)</td>
<td>7.40% (0.1%)</td>
<td></td>
</tr>
<tr>
<td>Triage category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>56.3% (0.8%)</td>
<td>66.5% (1.1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>81.82% (11.8%)</td>
<td>80.21% (13.1%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>35.50% (51.4%)</td>
<td>30.25% (49.5%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>21.86% (31.6%)</td>
<td>19.66% (32.2%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>29.92% (4.3%)</td>
<td>25.17% (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Day of week</td>
<td>0.68</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Monday</td>
<td>10.31% (14.9%)</td>
<td>9.20% (15.1%)</td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td>9.561% (13.8%)</td>
<td>8.470% (13.9%)</td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td>9.366% (13.6%)</td>
<td>8.124% (13.3%)</td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td>9.342% (13.5%)</td>
<td>8.197% (13.4%)</td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td>9.652% (14.0%)</td>
<td>8.676% (14.2%)</td>
<td></td>
</tr>
<tr>
<td>Saturday</td>
<td>10.172% (14.7%)</td>
<td>8.932% (14.6%)</td>
<td></td>
</tr>
<tr>
<td>Sunday</td>
<td>10.702% (15.5%)</td>
<td>9.526% (15.6%)</td>
<td></td>
</tr>
<tr>
<td>Season</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td>17.322% (25.1%)</td>
<td>15.515% (25.4%)</td>
<td></td>
</tr>
<tr>
<td>Autumn</td>
<td>17.730% (25.7%)</td>
<td>15.053% (24.5%)</td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>16.940% (24.5%)</td>
<td>15.218% (24.9%)</td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>17.113% (24.8%)</td>
<td>15.341% (25.1%)</td>
<td></td>
</tr>
</tbody>
</table>

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management.\textsuperscript{10,11} Expanding the capacity to admit patients who present to EDs is one of the major challenges in dealing with overcrowding.\textsuperscript{13} Codde et al.\textsuperscript{13} and Han et al.\textsuperscript{13} attest that even the most efficient ED cannot do any better if the volume and complexity of presentations increase, and inpatient beds are not available to enable transfer out of the ED. The level of access block experienced in the year after the new ED opened at Hospital A, B and C was 46%, 40% and 42% respectively. This is over two and half times higher than the access block of 16% identified by Fatovich et al.\textsuperscript{14} at the Royal Perth Hospital. This is a concerning finding for these hospitals and the wider community and is possibly reflective of a lack of inpatient bed numbers that accompanied the new ED opening. The high level of access block has implications beyond the immediate crowding effect. For example, a US study showed an increased mortality rate (of 2%) and longer hospital LOS (of approximately three additional days) for patients boarded in the ED for more than 12 and 24 h respectively.\textsuperscript{15} A more crowded ED has implications for the ability of a hospital to deal with surge capacity.\textsuperscript{11} The American College of Emergency Physicians (ACEP) defines surge capacity as the ‘healthcare system’s ability to manage a sudden or rapidly progressive influx of patients within the currently available resources at a given point in time’.\textsuperscript{12} For these reasons, whole of hospital and health service area approaches are needed to manage crowding and growth in service issues. Strong support from hospital managers and decision makers to address problems outside the ED is required to do this.\textsuperscript{10,13,33}

Clinical importance

Our main findings indicate that opening a new ED alone (i) did not improve overcrowding issues such as ambulance off-load time, ED LOS and access block at the hospital closest (Hospital A), (ii) did improve in-hospital mortality rates and (iii) had a strong effect at the hospital furthest away (Hospital B). The first finding is consistent with other reports describing the effect of new/expanded...
EDs opening in the United States. One study describing the effect of a new 96 room + 2 trauma bay ED reported increases in patient volume (by 11.5%), admission rate (from 27% to 29%) and average ED LOS for all patients (from 4 to 4.5 h) and admitted patients (from 6.5 to 7.5 h). Other reported outcomes that improved were patient and staff satisfaction, decreases in staff turnover and decreased need for ambulance diversion. These latter outcomes were not accompanied with pre-measures so it is difficult to interpret these findings.

Figure 2 Per cent ambulance offload time exceeding 30 min: Hospital A and Hospital B. (---), Hospital A OL 30 per cent; (---), LCL from Hosp_A_per cent OL30-Model_1; (---), UCL from Hosp_A_per cent OL30-Model_1; (---), predicted value from Hosp_A_per cent OL30-Model_1; Hospital B OL 30 per cent; (---), LCL from Hosp_B_per cent OL30-Model_1; (---), UCL from Hosp_B_per cent OL30-Model_1; (---), predicted value from Hosp_B_per cent OL30-Model_1.

Figure 3 Emergency department (ED) length of stay (LOS): Hospital A and Hospital B.
Another, more recent before and after study examined the effect of an ED expansion (from 28 to 53 beds) in the United States on ambulance diversion. Results from that study identified an increase in patient volume, but no significant change in time spent in the ED or number of ambulance diversions (approx 2) per month. Additionally, total and admission hold time (time waiting for ward bed) increased (total admission time: pre: 4.6 to post:

Table 6 Summary of time series ARIMA modelling testing the effect of opening ED on offload time, ED LOS and access block

<table>
<thead>
<tr>
<th>Model summary</th>
<th>Outcome</th>
<th>Model summary</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital A</td>
<td>% offload time &gt;30 min</td>
<td>0.098</td>
<td>0.142</td>
</tr>
<tr>
<td></td>
<td>MAPE</td>
<td>82.5</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td>Normalised BIC</td>
<td>3.7</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>Estimated intervention effect†</td>
<td>0.54</td>
<td>5.13</td>
</tr>
<tr>
<td></td>
<td>Standard error</td>
<td>0.69</td>
<td>3.13</td>
</tr>
<tr>
<td></td>
<td>T-test statistic</td>
<td>0.79</td>
<td>4.91</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>0.432</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital B</td>
<td>% offload time &gt;30 min</td>
<td>0.34</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>MAPE</td>
<td>84.8</td>
<td>47.02</td>
</tr>
<tr>
<td></td>
<td>Normalised BIC</td>
<td>4.90</td>
<td>9.46</td>
</tr>
<tr>
<td></td>
<td>Estimated intervention effect†</td>
<td>12.44</td>
<td>18.32</td>
</tr>
<tr>
<td></td>
<td>Standard error</td>
<td>1.42</td>
<td>3.58</td>
</tr>
<tr>
<td></td>
<td>T-test statistic</td>
<td>8.74</td>
<td>11.15</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†Estimated change in outcome measures after intervention compared with before, that is, time of opening the new ED; values less than 1 indicate reduction. ARIMA, Autoregressive Integrated Moving Average; BIC, Bayesian Information Criteria; ED, emergency department; LOS, length of stay; MAPE, mean absolute percentage error.
5.6 h; time waiting for an admission bed: pre: 3 to post: 4.1 h).

The new/expanded ED described in previous reports were from facilities in the United States from Level I and Level II trauma centres. Healthcare systems in the United States differ to those in Australia, in terms of specialisation of services and funding arrangements. These factors make further comparisons with these studies and settings difficult.

The second main finding indicates that despite worsening ED and hospital outcomes, the mortality rate dropped from one year to the next at both hospitals. In-hospital mortality rates in our study sites were higher than the national average of 1.3%. It may be that the reduction in overall numbers admitted to Hospitals A and B via the ED allowed for a more ‘holistic’ care focus that resulted in a lower mortality rate in the year after the new ED opened. There is also the possibility that with such short in-hospital LOS (2 days in our study vs 6.5 days for all Australian public hospitals, excluding same day separations), some people were discharged too early, died elsewhere and were not captured in this study.

The third main finding (worse outcomes at the hospital furthest away) has not been described in the literature in the context of a new ED opening. We put forward that had the new ED not opened, Hospital A (the closest hospital) would have followed similar trends to Hospital B, and outcomes might have been worse. It could be suggested that opening the new ED at Hospital C had a ‘stabilisation effect’ on Hospital A during the first year of the new ED’s operation. Interestingly, demand outgrowing additional ED capacity within 1 year of opening has been mentioned elsewhere.

In order to meet the growing demand on healthcare resources, the Australian Government (through the National Partnership Agreement) has committed to provide funding exceeding $3 billion for new subacute beds, to meet ED and elective surgery targets and for capital and recurrent projects to improve access for patients accessing public hospital services. Regarding the National Emergency Access Target (NEAT), it is expected that, following a staged annual increase, by 2015, 90% of ED presentations should be admitted, transferred or discharged within 4 h. In meeting these targets, the impact of additional beds and services in their much anticipated ability to provide more specialised and extensive healthcare to the surrounding community warrants evaluation.

Limitations

Several limitations pertain to this study. First, this study was limited to the impact on the two pre-existing public hospitals and did not include the effect on the three smaller private hospitals within the region. This option was considered at study inception; however, data captured differences would not have enabled analysis for these private facilities. Also, the recognised health service network within the region consists of 10 public hospitals. There may have been a network effect that extended beyond the two sites included in this study. Second, this was a retrospective analysis of prospectively collected data. There may have been inaccuracies within the data provided; however, data cleaning measures were implemented. Third, due to the large volume of data analysed, statistical significance may not necessarily relate to clinical significance. However, given that not all outcomes were significant indicates that sample size was not the only factor determining significance. Fourth, our study was limited to the impact of opening additional ED beds only. Because no accompanying hospital beds were opened at the same time, the interpretation of our findings should consider this fact. However, this is perhaps the first study that assesses the healthcare delivery outcomes using linked population-based databases in Australia to examine the effect of a new ED opening as most of the previous such assessments were reported from the United States.

Conclusion

The aim of this study was to investigate the impact of opening a new ED on patient and regional healthcare delivery systems outcomes. Our data indicated that an additional ED within the region saw an increase in the total volume of ED presentations at a rate far greater than local population growth, suggesting it either tapped into a previously unmet need within the local community or resulted in a shifting of activity from one sector to another. While a new ED could ease the pressure on workload, careful monitoring by appropriate healthcare service planners is vital as the dynamics of healthcare delivery changes occur in a geographical region may not be a simple equation. We support the inherent need to take a ‘whole of hospital’ and ‘whole of health service area’ approach to solving crowding issues. Future research should explore and describe factors surrounding met or unmet service need with the use of geo-coding mapping and analysis to understand where patients travel from to reach their chosen hospital and account for economic and service delivery implications. Future studies should also examine patient decision-making practices regarding reasons for presenting to a new or pre-existing ED as well as evaluations of other service delivery initiatives aimed at improving workload practices.
Acknowledgements

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References

Underlying heart disease and microbiological spectrum of adult infective endocarditis in one Chinese university hospital: a 10-year retrospective study

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Key words
infective endocarditis, congenital heart disease, degenerative valvular disease, rheumatic heart disease, viridans group streptococcus.

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Abstract

Background and Aim: To identify the underlying heart disease and microbiological pathogen associated with infective endocarditis (IE) in Chinese patients in one university hospital over a 10-year period.

Methods: We recruited 115 adult patients admitted to Peking University First Hospital from 2002 to 2011 who were diagnosed with definite IE. Statistical analysis was performed to analyse data on demographics, clinical and laboratory findings, as well as microbiological pathogens.

Results: The most common underlying heart diseases for IE were congenital heart disease (24.3%) followed by degenerative valvular disease (17.4%). Aortic (44.3%) and mitral (43.5%) valves were most frequently affected. The right-sided IE cases were all found in patients with congenital heart disease. The age of patients was younger in right-sided cases than that in left-sided ones ($P = 0.001$). There was no difference in the mortality among groups with different underlying heart disease ($P = 0.841$). Forty-four (38.3%) patients were infected with viridans group streptococci. The isolation rate of staphylococci in right-sided IE was higher than that in the left-sided IE group ($P = 0.021$). More than 85% of streptococci were susceptible to β-lactams.

Conclusions: Congenital heart disease and degenerative valvular disease have overtaken rheumatic heart disease as the major underlying heart diseases associated with IE. Viridans group streptococci are the most common microbial cause of IE.

Introduction

Infective endocarditis (IE) is one of the most severe systemic infectious diseases characterised by high morbidity and mortality. Despite advances during the past century in diagnosis, drug therapy and surgical treatment, the in-hospital mortality still remains around 20%.1–3 While the annual incidence of 25–70 cases per 1 million persons per year has been stable for the past several years, the demographic profile of patients with IE has evolved continuously since the first modern clinical description of
this disease in the 19th century. A decreasing proportion of IE patients with rheumatic heart disease (RHD) parallels an increase in elderly patients with degenerative valvular diseases (DVD). The proportion of adult IE patients with congenital heart disease (CHD), especially cyanotic CHD, has reportedly increased significantly in developed countries. RHD used to be the predominant underlying heart disease in IE patients in China. However, patients with CHD nowadays are surviving longer than before.

Unfortunately, there are limited data on the clinical epidemiology of IE in China. It is also unknown whether there have been any recent changes in the pathogens causing IE and their antibiotic susceptibility patterns. The aim of this study, therefore, was to identify the underlying heart diseases associated with IE, the epidemiology of causative pathogens and their antibiotic susceptibility in cases from one Chinese university hospital over the past 10 years.

Methods

Patient selection and data collection

Peking University First Hospital is a 1368-bed teaching hospital in Beijing, China. It includes departments of internal medicine, surgery, paediatrics and obstetrics and gynaecology. All inpatient data in our hospital are entered on to an electronic medical records database. In this study, we reviewed the demographics, clinical, laboratory, echocardiography, pathology and microbiological features of consecutive patients diagnosed with IE between 1 January 2002 and 31 December 2011. Each patient identified as endocarditis in the database was reviewed by one investigator and classified into definite, possible or rejected IE according to the modified Duke criteria. Another two senior investigators independently reviewed and classified cases selected at random. There was 100% agreement on case classification. Finally, 138 patients who were identified as definite IE were recruited from the Departments of Cardiovascular Disease and Pediatrics. Among the study, 23 cases younger than 18 years of age were excluded, leaving 115 adult patients who were included in this study. The laboratory data (white blood cell count, haemoglobin, C reactive protein, albumin and serum creatinine) were collected either on admission or on the presence of fever during hospitalisation.

Microbiologic technique and bacterial susceptibility test

The microbiology laboratory in Peking University First Hospital is a national reference laboratory in quality control management of clinical laboratory of the Ministry of Health. All the blood taken from recruited cases was incubated in BD BACTEC FX automated blood culture system (BD Company, USA). Minimal inhibitory concentrations were determined for each isolate according to the broth microdilution method specified by the Clinical and Laboratory Standards Institute.

Cases definitions

Immune suppression was defined as one of the following conditions: (i) current use of ≥10 mg equivalent of prednisone per day for at least 1 month, (ii) chemotherapy or radiation therapy within last 3 months, (iii) human immunodeficiency virus infection, (iv) primary or secondary immunodeficiency syndrome, (v) cancer and (vi) solid organ or bone marrow transplantation. Nosocomial acquisition of IE was defined by the onset of signs and symptoms of IE in patients who had been hospitalised for 48 h or longer, or whose presumed source of acquisition was related to medical practice.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 statistical software (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as medians and interquartile range. Categorical variables were presented as frequencies and percentages of the specified group. Comparisons between different groups of underlying heart disease were made with the χ² test or Kruskal–Wallis test as appropriate. Fisher’s exact test (two tailed) was used if the expected count in any cell was <5. Mann–Whitney test was used in the comparison between the group of right-sided and the left-sided IE. P-value <0.05 was considered statistically significant.

Results

General characteristics

The total number of admission to hospital during 2002–2011 was 36,560 patients. The definite IE incidence was 2.7 ± 0.6 cases/10,000 patients-year. Another nine cases treated as IE but did not fulfil the Dukes criteria for definite IE were classified as possible IE during this period. This study included 115 definite IE patients: 82 males and 33 females. Seventeen cases (14.8%) were transferred from other hospitals.

The general characteristics of all collected cases were shown in Table 1. Fifty-two patients denied any previous heart disease. All the 28 patients with CHD were under 65 years of age and consisted of 14 patients with ven-
tricular septal defect (VSD), 4 patients with patent ductus arteriosus (PDA), 9 patients with bicuspid aortic valve and 1 with transposition of great arteries. DVD in patients mainly presented as mitral valve prolapse (12/115 cases) and calcified aortic valve stenosis (8/115 cases). Of the 115 patients, 105 (91%) had community-acquired and 10 (9%) had nosocomial infection. Twelve patients (10%) died in hospital, and 11 patients (10%) discontinued treatment when they were in critical conditions and discharged themselves from hospital.

Findings on presentation

The major presenting symptoms, signs, laboratory findings and sites of vegetation were summarised in Table 2. According to their history of heart disease, patients were categorised into one of four groups: CHD group, RHD group, DVD group and no heart disease (NHD) group (patients without previous heart disease). IE patients with underlying heart diseases were also analysed temporally based on their admission date to the hospital: 2002–2006 and 2007–2011 (Fig. 1). The most typical symptom/sign at onset was fever, followed by cardiac murmur and anaemia. One hundred and five patients (91%) had fever, and the other ten patients had paroxysmal nocturnal dyspnoea as initial presentation. Thirty-seven patients (32%) had embolic events, involving major artery vascular (renal artery, splenic artery, pulmonary artery and mesenteric artery), intracranial haemorrhage and Janeway lesions. There were no significant differences among four groups in clinical findings and outcome.

The most common site of vegetation was aortic valve, in which 51 cases (44%) involved aortic valve alone or along with mitral valve. All the right-sided IE was found in patients with CHD. Table 3 showed that the age of patients was younger in right-sided cases than that in left-sided cases. Lower level of albumin ($P = 0.015$) and higher CRP level ($P = 0.041$) were found in the patients with right-sided IE compared with those in the left-sided IE group. No significant difference was found in the mortality between two groups.

Microbiological aetiology

Of the 115 cases, 78 (68%) patients had positive blood cultures. The causative organisms were not significantly different among four groups (Table 2). Streptococcus spp. was the most frequently isolated pathogen in this series, with viridans group streptococci found in 44 cases (44/78, 56.4%), followed by Streptococcus bovis in seven cases. Staphylococcus species were found in 14 cases. Only three patients were infected with Gram-negative bacteria: Serratia marcescens (two patients) and Haemophilus paraphrophilus (one patient) (Table 4). All patients with negative cultures also had negative serology for Brucella and Legionella species. Among all 37 culture-negative cases, 31 (84%) had received antibiotics before blood collection. The percentage of staphylococcus isolation in the

Table 1 General characteristics of 115 patients with infective endocarditis (IE)

<table>
<thead>
<tr>
<th>Patient information</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD) (years)</td>
<td>46.4 ± 15.1</td>
</tr>
<tr>
<td>Male/female</td>
<td>82/33</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (12.2)</td>
</tr>
<tr>
<td>Immune suppression, n (%)</td>
<td>17 (14.8)</td>
</tr>
<tr>
<td>History of heart diseases</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease, n (%)</td>
<td>28 (24.3)</td>
</tr>
<tr>
<td>Rheumatic heart disease, n (%)</td>
<td>15 (13.0)</td>
</tr>
<tr>
<td>Degenerative valvular disease, n (%)</td>
<td>20 (17.4)</td>
</tr>
<tr>
<td>No heart disease, n (%)</td>
<td>52 (45.2)</td>
</tr>
<tr>
<td>Implanted permanent pacemaker, n (%)</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>Type of endocarditis</td>
<td></td>
</tr>
<tr>
<td>Native valve, n (%)</td>
<td>103 (89.6)</td>
</tr>
<tr>
<td>Prosthetic valve, n (%)</td>
<td>12 (10.4)</td>
</tr>
<tr>
<td>Presumed source of acquisition</td>
<td></td>
</tr>
<tr>
<td>Haemodialysis, n (%)</td>
<td>5 (4.3)</td>
</tr>
<tr>
<td>Vascular prosthesis, n (%)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Dental procedure, n (%)</td>
<td>8 (7.0)</td>
</tr>
<tr>
<td>Other or unknown, n (%)</td>
<td>100 (87.0)</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>12 (10.4)</td>
</tr>
<tr>
<td>Give up treatment, n (%)</td>
<td>11 (9.6)</td>
</tr>
<tr>
<td>Surgery, n (%)</td>
<td>45 (39.1)</td>
</tr>
</tbody>
</table>

Figure 1 Distribution of underlying heart disease in 115 infective endocarditis cases in two time periods. RHD, rheumatic heart disease; CHD, congenital heart disease; DVD, degenerative valvular disease; NHD, no heart disease. □, 2002–2006; ■, 2007–2011.
right-sided IE was higher than that in the left-sided IE group ($P = 0.021$) (Table 3). The results of antibiotic susceptibility testing for staphylococci and streptococci are shown in Table 5. There were two strains of *Staphylococcus aureus* and one strain of *Staphylococcus epidermidis* that were resistant to oxacillin. No noticeable change was observed in either distribution or antibiotic sensitivity of organisms between the period of 2002–2006 and 2007–2011 (data not shown).

**Discussion**

The patients in this study showed similarly clinical features to those in previous reports. Middle-aged men were the most commonly affected group, and the site of vegetation tended to be predominantly located on the left side. The percentage of patients with prosthetic valves in our study is lower than other published reports as was the in-hospital mortality. One feature of this study is that the proportion of IE patients with RHD was lower than for CHD and DVD. The temporal distribution also showed the occurrence of IE with RHD was less than the other two underlying heart diseases in the period of 2007–2011. Some other data from tertiary care settings in Beijing, Hongkong and Taiwan recruiting IE cases during 1995–2007 display a similar declining trend in the proportion of RHD accompanied by rising of CHD and DVD. This change parallels the declining incidence of RHD in China over recent years, especially in urban areas. Cheng noted that RHD has declined progressively from 50% of the total hospital cardiac admissions in Shanghai in 1948–1957 to 2% in 2000–2005, which has been explained by improvements in living conditions.

On the other hand, 24% of patients in this study had underlying CHD. VSD, PDA and bicuspid aortic valve/aortic stenosis were the most common underlying diseases, which are considered high-risk lesions for IE. The more widespread application of paediatric surgery in...
the recent decades has meant that more CHD patients are surviving to adulthood in China. Increasing rates of CHD among adults has also been reported in developed countries, such as UK20 and Canada.21 Mitral valve prolapse and calcified aortic stenosis constituted the pathology of IE in patients with DVD. Mitral valve prolapse is now recognised as a common risk factor for IE in developed countries3,22 with broad consequences.23,24 Recently, many investigators report that staphylococci have overtaken viridans group streptococci as the predominant causative agent for IE,13,17,25 especially in children.26 The isolation rate of staphylococci can be as high as 30–40% among IE patients. In contrast, viridans group streptococci (44/78, 56.4%) was the leading pathogen in our study, perhaps reflecting the fact that most cases in our study were community acquired.

The isolation rate of staphylococci can be as high as 30–40% among IE patients. In contrast, viridans group streptococci (44/78, 56.4%) was the leading pathogen in our study, perhaps reflecting the fact that most cases in our study were community acquired. More than 85% of Streptococcus spp. were susceptible to β-lactams in our study, which is similar to other reports from community-acquired bacteraemia and IE.27–29 Among staphylococci, 80% of strains were sensitive to oxacillin. There are several limitations to our study. The sample size is relatively small compared with other series. Multiple selection biases might be inevitable. The third limitation is higher percentage of culture-negative cases. Most of these cases received antibiotics prior to hospitalisation, which is a problem seen elsewhere in China.16

## Conclusion

CHD and DVD have surpassed RHD to be the dominant underlying heart disease with IE in the adult patients in this series. All right-sided IE cases are from CHD group, which is characterised by younger age and higher percentage of staphylococcal isolation. Viridans group

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparison of clinical characteristics between patients with left and right-sided infective endocarditis (IE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left-sided (n = 101)</td>
</tr>
<tr>
<td>Age, median (IQR) (years)</td>
<td>53.4 (39.0–64.0)</td>
</tr>
<tr>
<td>Prosthetic valve, n (%)</td>
<td>12 (11.9)</td>
</tr>
<tr>
<td><strong>Clinical findings</strong></td>
<td></td>
</tr>
<tr>
<td>Fever, n (%)</td>
<td>93 (92.1)</td>
</tr>
<tr>
<td>Cardiac murmur, n (%)</td>
<td>89 (88.1)</td>
</tr>
<tr>
<td>Anaemia, n (%)</td>
<td>66 (65.3)</td>
</tr>
<tr>
<td>Renal haematuria, n (%)</td>
<td>50 (49.5)</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>41 (40.6)</td>
</tr>
<tr>
<td>Embolism, n (%)</td>
<td>35 (34.7)</td>
</tr>
<tr>
<td><strong>Laboratory findings</strong></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, median (IQR) (g/dL)</td>
<td>10.5 (9.3–12.6)</td>
</tr>
<tr>
<td>WBC, median (IQR) (x10^9/L)</td>
<td>7.6 (6.4–11.0)</td>
</tr>
<tr>
<td>CRP, median (IQR) (mg/L)</td>
<td>35.8 (18.8–64.7)</td>
</tr>
<tr>
<td>Alb, median (IQR) (g/L)</td>
<td>34.5 (30.4–37.9)</td>
</tr>
<tr>
<td>Serum creatinine, median (IQR) (umol/L)</td>
<td>83.0 (72.5–110.5)</td>
</tr>
<tr>
<td><strong>Organism</strong></td>
<td></td>
</tr>
<tr>
<td>Streptococci, n (%)</td>
<td>47 (46.5)</td>
</tr>
<tr>
<td>Staphylococci, n (%)</td>
<td>8 (7.9)</td>
</tr>
<tr>
<td>Other organisms, n (%)</td>
<td>11 (10.9)</td>
</tr>
<tr>
<td>Culture negative, n (%)</td>
<td>34 (33.7)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
</tr>
</tbody>
</table>

| Mortality, n (%) | 10 (9.9) | 2 (16.7) | |

Alb, albumin; CRP, C-reactive protein; IQR, interquartile range; WBC, white blood cell.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Microbiology aetiology in 78 infective endocarditis patients with positive blood culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism</td>
<td>No. strains (%)</td>
</tr>
<tr>
<td>Streptococcus spp.</td>
<td>51 (65.4)</td>
</tr>
<tr>
<td>Viridans group Streptococcus</td>
<td>44</td>
</tr>
<tr>
<td>Streptococcus bovis</td>
<td>7</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
<td>14 (17.9)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>12</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>13 (16.7)</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>3</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>2</td>
</tr>
<tr>
<td>Micrococcus sedentarius</td>
<td>3</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>2</td>
</tr>
<tr>
<td>Haemophilus paraphrophilus</td>
<td>1</td>
</tr>
<tr>
<td>Candida albican</td>
<td>1</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>1</td>
</tr>
</tbody>
</table>
strepococci are still the most frequently isolated pathogen of IE, but are still susceptible to most relevant antibiotics.

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The authors gratefully thank Dr Sainan Zhu (Department of Medical Statistics, Peking University First Hospital) for contribution in statistical analysis and thank Dr Jibing Yang (University of Michigan) for critical review of this manuscript.

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Health and well-being among physicians
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Key words
screening, physician, colonoscopy, PSA, mammogram.

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Abstract

Background and Aim: Physicians’ attitudes towards disease prevention are crucial. The purposes of this study are to examine the prevalence of cardiovascular risk factors and adherence to international preventive screening programmes by a group of physicians.

Methods: Online and paper format questionnaires were completed by a sample of 650 physicians from November 2010 to March 2011. The collected data included the main components of screening programmes, which are recommended in international guidelines.

Results: The data show that 30.5% of male physicians currently smoke, 19.4% are obese, 15.2% have hypertension, 38% are physically inactive and 10.9% have diabetes. Nearly all (95%) of the female participants and most (83%) of the male participants older than 45 years had never had a colonoscopy. Of the male physicians older than 55 years, 36.4% had never had prostate-specific antigen testing, and only 10.9% had undergone a digital rectal examination. Among the female physicians, 27.4% were obese, and 42% had never had a mammogram.

Conclusion: The prevalence of behavioural risk factors for cardiovascular disease is high among physicians. A substantial percentage of the practising physicians did not adhere to the age-specified preventive screening measures recommended in international guidelines.

Introduction

Prevention is considered a cornerstone in disease control. Several studies have demonstrated that many eligible patients do not receive recommended preventive services.1–9 Physicians play an important role in improving healthcare and containing its costs through effective patient counselling. Knowledge, attitude, skills, experiences, beliefs and values play fundamental roles in the behaviour of both physicians and patients.4–6,10–14 Physicians’ attitudes towards disease prevention are important because physicians are responsible for medical education; therefore, their degree of acceptance of these preventive strategies carries great weight. Physicians’ advice to patients will be more credible if they themselves practise the screening guidelines that they advocate and heed the lifestyle recommendations that they propose. Yet, few studies have investigated physicians’ adherence to preventive medicine guidelines in terms of their application of these guidelines to themselves.15–17

The aim of this study is to evaluate the adherence of physicians to preventive medicine guidelines and the application of such measures to themselves so as to identify the factors that predict compliance with the screening process.

Methods

This study was designed as a prospective questionnaire-based, cross-sectional survey that was carried out from November 2010 to March 2011 in the Kingdom of Saudi Arabia. The Institutional Review Board, College of Medicine has approved this study. We distributed a paper format questionnaire to four tertiary hospitals. In addition, we used the email address list of physicians registered in the Saudi Council for Health Specialties to distribute the electronic version of the survey. We prepared the electronic questionnaire and database of potential respondent email addresses using the Survey Monkey online survey instrument and emailed a link to the online questionnaire to each potential participant. The survey employed a skip logic pattern, allowing physicians to skip certain portions based on responses to preceding
questions. Potential respondents received two personal reminder emails if they did not respond to the initial survey within a week. If physicians expressed a desire not to participate in the survey, they did not receive any additional reminder emails. As an incentive, all sampled physicians could participate in a draw for two prizes. Data collected included the demographics and training background of participants and evaluated the main components of screening programmes, which are recommended in American guidelines, including bodyweight, blood pressure, diabetes, colorectal cancer, cholesterol and eye examination for glaucoma for all participants, as well as prostate-specific antigen (PSA) testing for male participants and breast and cervical cancer screening for female participants.18,19

We defined participants with diabetes as all those who had received a diagnosis of this disease from a physician, whether or not they were receiving treatment with insulin or oral hypoglycaemic medications. We defined respondents who had diabetes only during pregnancy as not having diabetes. We defined participants with hypertension as all those who had received a diagnosis of this condition from a physician, irrespective of antihypertensive treatment. We defined obesity as a body mass index (BMI) of 30 or greater, with BMI being determined from participants’ self-reported height and weight. We defined current smoking as daily or occasional consumption of at least one cigarette. Ethical approval was obtained from the ethics committee at King Khalid University Hospital. The research team approached all potential participants and obtained verbal consent from them. (Verbal consent rather than written consent was obtained because all participants were clinicians before enrolment in the study.) All potential candidates were free to decline participation or withdraw from the study at any time. To ensure confidentiality, subject numbers on the data collection sheets were used to identify subjects. The identity of participants has not been declared in any publication.

Statistical analysis

All analyses were conducted using SAS statistical software (SAS Institute, Cary, NC, USA). Descriptive statistics were computed for each item in the survey, using means for continuous variables and percentages for categorical variables. A Pearson exact Chi-squared test was performed to analyse the association between predictors and screening participation. Logistic regression was used to examine the association between the demographic variables and compliance with screening recommendations for colonoscopy and mammography. The joint effects of multiple independent predictors of screening participation were assessed using odds ratios (ORs) and 95% confidence intervals (CI) generated by multiple logistic regression analysis. Only variables with statistical significance \( P < 0.05 \) were entered in the final logistic regression models.

Results

We received 650 completed surveys: 380 paper format surveys and 270 online surveys. The overall response rate for the survey was 40.1%. As shown in Table 1, respondents were most likely to be middle-aged, and 21.8% of respondents were women. Almost 33% of all participants were internist physicians, and 42.6% had received their postgraduate training in North America or Europe.

Risk factors prevalence for cardiovascular disease among male physicians is shown in Figure 1. Regarding physical health characteristics, the mean BMI (± SD) of female physicians was 26.5 (± 4.7), but 27.4% were obese, as defined by a BMI score greater than 30. The mean BMI for male physicians was 27.4 (± 4.2), with 19.4% of them defined as obese. During the past month, only 62% of male physicians and 56% of female physicians had participated in physical activities other than their regular job. Among physicians who had ever smoked, 9.4% currently smoked daily, 8.1% smoked occasionally and 8.6% were ex-smokers. Female physicians were more likely to have never smoked than male physicians (89.2% vs 69.5%, respectively, \( P = 0.001 \)).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Female (%)</th>
<th>Male (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>142 (21.8)</td>
<td>508 (78.2)</td>
</tr>
<tr>
<td>Saudi nationality, n (%)</td>
<td>71 (50)</td>
<td>298 (58.7)</td>
</tr>
<tr>
<td>Age, n (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>24 (16.9)</td>
<td>83 (16.6)</td>
</tr>
<tr>
<td>35–45</td>
<td>81 (57)</td>
<td>210 (42)</td>
</tr>
<tr>
<td>46–55</td>
<td>34 (23.9)</td>
<td>152 (30.4)</td>
</tr>
<tr>
<td>&gt;55</td>
<td>3 (2.1)</td>
<td>55 (11)</td>
</tr>
<tr>
<td>BMI, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>53 (72.6)</td>
<td>204 (80.6)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>20 (27.4)</td>
<td>49 (19.4)</td>
</tr>
<tr>
<td>Location of postgraduate training, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>67 (48.2)</td>
<td>175 (35.1)</td>
</tr>
<tr>
<td>Europe</td>
<td>15 (10.8)</td>
<td>94 (18.8)</td>
</tr>
<tr>
<td>North America</td>
<td>22 (15.8)</td>
<td>141 (28.3)</td>
</tr>
<tr>
<td>Other</td>
<td>35 (25.2)</td>
<td>89 (17.8)</td>
</tr>
<tr>
<td>Specialty, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Medicine</td>
<td>26 (18.3)</td>
<td>144 (28.7)</td>
</tr>
<tr>
<td>Surgery</td>
<td>9 (6.3)</td>
<td>89 (17.7)</td>
</tr>
<tr>
<td>Paediatric</td>
<td>15 (10.6)</td>
<td>68 (13.6)</td>
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<tr>
<td>Obstetrics and gynecology</td>
<td>52 (36.6)</td>
<td>26 (5.2)</td>
</tr>
<tr>
<td>Other</td>
<td>40 (28.2)</td>
<td>175 (34.9)</td>
</tr>
</tbody>
</table>

BMI, body mass index.

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Although the majority of both sexes had received hepatitis B vaccinations (86.5% of male physicians and 88.5% of female physicians), only half of male respondents and 59.1% of female respondents had received clinical eye examinations in the past 2 years.

The prevalence of hypertension was 15.2% among participants (Fig. 1). Among those not known to have elevated blood pressure or hypertension, 14.3% had not had their blood pressure checked in the past 2 years. Diabetes was prevalent in 10.9% of participating physicians (Fig. 1). Twenty-seven per cent of those with no history of diabetes had not had their blood sugar measured within the past 3 years. All but 16.5% of men and 18.8% of women had their cholesterol measured in the past 5 years.

Half of male and female respondents older than 45 years had never undergone an occult blood stool examination. Most (83%) of male and nearly all (95%) of female participating physicians had never undergone a colonoscopy (Figs 2,3). Among female physicians older than 45 years of age, 42% had never received a mammogram (Fig. 3), and only 31.6% had received mammograms within the past year. Among female physicians who were 45 years and younger, 52.8% had never undergone a Pap smear compared with 21.1% of those older than 45 years of age. Forty per cent of married female participants had undergone a Pap smear within the past 3 years. Among male physicians older than 55 years of age, 58.2% had never received a digital rectal examination, and 36.4% had never had a PSA test (Fig. 2). Only 10.9% had received a digital rectal examination, and 45.5% had undergone a PSA test within the past year.

A logistic regression was conducted, with compliance colorectal screening as the dependent variable. Gender, specialty, place of postgraduate training, method of survey and nationality served as predictors. The univariate analysis identified a trend of female physicians being less compliant with screening colonoscopy, with an OR of 6.8 (95% CI, 0.9–51.5). The multivariate analysis
revealed that subspecialty, method of survey, place of postgraduate training and nationality were not significant. The multivariable model for mammogram participation revealed that nationality, method of survey and subspecialty did not have an impact on compliance of female physicians with the screening; however, those who had local training were less likely to undergo a screening mammogram, with an OR of 0.434 (95% CI, 0.273–0.690).

Discussion

Although screening is widely touted by authoritative healthcare groups as a valuable preventive tool for certain diseases, and evidence exists of its cost-effectiveness, screening rates remain far below those necessary to attain a reduction in mortality.20–27 Numerous barriers to screening have been identified, including poor patient compliance, lack of provider encouragement, lack of time, lack of awareness of the importance of screening, patients’ lack of motivation, patient dislike or refusal, and lack of healthcare coverage.4–11 Several studies have reported that lack of healthcare provider recommendation is the primary reason for low cancer screening participation.12–17 Because physician awareness and belief in the importance of screening intervention are paramount, we decided to turn the tables and make physicians the focus of the present study by assessing their adherence to screening programmes among themselves.

Cancer, heart disease and stroke are also among the most common causes of death in physicians.28 Therefore, physicians need to realise the benefits of primary prevention and engage themselves in comprehensive cardiovascular risk reduction. The healthcare systems also should create an environment supportive of risk factor change, including long-term reinforcement of adherence to lifestyle and drug interventions among healthcare providers.

Rates of smoking have dropped over the years in developed countries among the general population and healthcare providers. However, current statistics indicate that smoking is a major health problem that continues to grow in developing countries. Physicians in the present study reported higher rates of smoking (17.3% current smokers; 8.6% ex-smokers) than those of Canadian and American physicians (3.3% and 4% respectively).15 This finding may reflect the smoking pattern of the Saudi general population.29 Similar high rates of smoking among physicians have been reported in China and Europe.30–32 The majority of female physicians included in this article were nonsmokers. This finding can be explained by the culture of the study area, where there is a social stigma associated with smoking by females.

Blood pressure screening is recommended every 2 years for adults up to 65 years, then yearly. Among those participants not known to have elevated blood pressure or hypertension, 14.3% had not had their blood pressure checked in the past 2 years, whereas 15.2% of participants were already known to have hypertension.

Although screening for colorectal cancer with colonoscopy has been endorsed in several guidelines,21 half of male and female respondents older than 45 years had never had an occult blood stool examination. Previous research has revealed that individuals with a higher...
level of education and those with better health status are less likely to undergo a screening colonoscopy. In the present study, 95% of female physicians and 83% of male physicians older than 45 years had never had a colonoscopy. The stigma or awkwardness of having a colonoscopy may explain why many informed individuals choose not to undergo this procedure.

Additional studies are needed to examine the health and well-being of the Saudi communities. Similarly, we need to address methods to improve screening utilisation among healthcare providers and general public. Physicians may fail to adhere to the guidelines that they themselves provide to their patients. Some possible barriers that prevent healthcare professionals’ adherence to screening guidelines are a lack of time, a lack of familiarity with the guidelines, disagreement with the guidelines, low self-efficacy and culture-related factors. This low adherence to screening guidelines by physicians may also negatively influence the adoption and implementation of such screening guidelines among their patients. This poor adherence may improve with interventions directed at both physicians and institutions. These interventions may include the provision of more educational resources to physicians in all specialties, the adoption of culture-oriented screening methods and the incorporation of recommended guidelines into a mandatory routine medical assessment protocol for all healthcare providers, as has been carried out for the hepatitis B vaccination. Interventions should also encourage the use of a primary care physician among all physicians. Promoting physicians’ adoption of a healthy lifestyle will benefit not only physicians, but also their patients.

Several limitations should be considered when interpreting the findings of our study. As with any self-reported survey, the data are subject to recall, incorrect interpretation of questions, nonresponses and overreporting of screening status. These limitations may lead to an overestimation of the true rate of compliance of physicians to screening practices. Although administering an online survey has the potential to increase the ease of response within a target population, some members of the target population in the present study may have not participated because of their discomfort with online interactions. However, we adjusted for the methods of survey in our statistical analysis. A notable limitation of our study was the reliance of the survey data on self-reported risk factors. Surveys may underestimate disease conditions, such as diabetes, hypertension obesity or other cardiovascular risk factors. Comparisons of measured and self-reported risk factors have suggested that self-reported values may underestimate the true prevalence. Therefore, these risk factors may even be more prevalent than our findings suggest.

Finally, we did not examine the impact of physician adherence to screening guidelines on patient care.

**Conclusion**

We find that physicians’ adherence to recommendations among themselves is low. Physicians’ perceptions and beliefs should be fully understood in efforts to foster their adherence to international prevention recommendations among themselves and their patients.

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Does subjective evaluation of the frequency of salty food intake predict the risk of incident hypertension? A 4-year follow-up study in a middle-aged population

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Key words hypertension, questionnaire, risk factors, salty food intake.

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Abstract

Background: Excess salt intake increases blood pressure (BP). Identifying individuals with excess salt intake is, therefore, important for the prevention of hypertension.

Aim: To examine the predictive value of subjective evaluation of salty foods intake for the risk of incident hypertension in a middle-aged population.

Methods: A total of 970 non-hypertensive workers (mean age, 44 ± 6 years) was followed for a maximum period of 4 years, and their BP was measured annually. At baseline, all participants were asked about their subjective frequency of salty foods intake (seldom, sometimes or always), and they were divided into three groups according to their answers. Hypertension was defined as systolic/diastolic BP ≥ 140/90 mmHg or use of antihypertensive medications.

Results: There were no significant differences in the 4-year cumulative incident rate of hypertension among the ‘seldom’, ‘sometimes’ and ‘always’ groups (15.8%, 14.3% and 10.3%, respectively, log–rank test \( P = 0.44 \)). In a multivariate Cox proportional hazards model, age, body mass index and the baseline BP category were independent predictors for developing hypertension, whereas the frequency of salty foods intake was not a predictor (adjusted hazard ratio (95% confidence interval), 0.99 (0.64–1.54) in the ‘sometimes’ group and 0.64 (0.33–1.28) in the ‘always’ group as compared with the ‘seldom’ group).

Conclusion: The subjective evaluation of salty foods intake did not predict the 4-year risk of incident hypertension in this study population. Further investigations with a longer follow-up period are needed to clarify whether the present insignificant results are maintained for more than 4 years.

Introduction

Excess salt intake is well known to increase blood pressure (BP),1,2 thus increasing the risk of incident hypertension. Several clinical studies have also shown that salt reduction decreases BP in both hypertensive and normotensive individuals.3 Because hypertension is one of the major risk factors for cardiovascular disease (CVD), stroke and chronic kidney disease,1,4–6 the identification of individuals with excess salt intake has been considered important for the prevention of hypertension and subsequent hypertension-related health problems.

There are several objective and reliable methods for evaluating salt intake, such as the measurement of urinary sodium excretion, a record of consumed foods and food weighing.7 However, fully utilising these methods in the daily clinical practice and general health examination fields is difficult because they are complicated, time-consuming and require particular expertise. On the other hand, subjectively evaluated information on salt intake can be easily obtained by medical interviews and self-reporting questionnaires, even in a high throughput environment. Hashimoto et al. reported that urinary sodium excretion, as a reflection of actual salt intake, was significantly increased in subjects reporting a salt preference compared with subjects not reporting a salt preference.8 We recently reported that the frequency of salty food intake measured subjectively was positively associated with urinary sodium excretion in individuals who underwent a general health examination.9 These findings suggest that subjective measurement of salt intake could be a useful tool for estimating the actual salt intake. However, such information was not associated

Funding: None.
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with the BP levels in those previous studies, possibly because of the cross-sectional nature of the studies.

To clarify whether subjective information on the frequency of salty food intake predicts future development of hypertension, we conducted a longitudinal, observational study in a work-site based, middle-aged population.

**Methods**

**Study population**

The baseline survey was conducted during an annual general health examination at a precision equipment manufacturer in Kanagawa, Japan, in 2005. A total of 1169 workers agreed to participate in the present study and underwent health examination. Of the 1169 workers, those with hypertension (n = 186) or those who had any history or presence of CVD (n = 3) were excluded from the study. Individuals who did not completely respond to a questionnaire regarding their lifestyle were also excluded (n = 10). Finally, 970 workers (age range, 35–63 years old; 897 men) participated in the present study. This study protocol was approved by the ethics committee of Nippon Medical School, and all participants gave informed consent.

**Baseline survey**

All participants underwent anthropometric and BP measurements and blood sampling. All measurements were conducted in a temperature-controlled room, maintained at 22 ± 2°C. The brachial systolic and diastolic BP were measured by well-trained staff members using a mercury sphygmomanometer with the optimal cuff size for each subject’s arm circumference. The BP was determined using the right arm of a seated subject, after at least 5 min of rest. The first and fifth Korotkoff sounds were recorded to determine the systolic and diastolic BP respectively. The BP was measured twice with a 1-min interval between measurements, and each BP level was categorised according to the 2009 Japanese Society of Hypertension Guidelines for the Management of Hypertension

The outcome of the present study was the development of hypertension. The BP of the subjects was measured, and the initiation of antihypertensive medication was followed annually for a maximum period of 4 years (2006–2009). The follow-up was censored when the outcome was ascertained or the subjects were lost to follow-up.

**Follow-up examinations**

Blood samples were obtained from the antecubital vein after overnight fasting. Standard enzymatic methods were used to measure the serum total cholesterol, triglyceride, uric acid and plasma glucose levels. The serum high-density lipoprotein (HDL) cholesterol level was measured using the direct method. Dyslipidaemia was defined as total cholesterol level ≥220 mg/dL, triglyceride level ≥150 mg/dL or HDL cholesterol level <40 mg/dL. Hyperuricaemia was defined as a uric acid level ≥7.0 mg/dL. Impaired fasting glucose/diabetes was defined as a fasting plasma glucose concentration ≥110 mg/dL.

A self-reporting questionnaire was used to collect the participants’ lifestyle data, including that on their smoking status, exercise habits, alcohol intake and the frequency of salty food intake. Smoking status was categorised as either current or non-smoking. Current smoking was defined as regular cigarette consumption (at least once daily) at the time of study participation. Regular exercise was defined as continuous exercise for at least 15 min for 3 or more days per week for at least 1 year. Weekly alcohol intake was calculated by combining the amount of alcohol consumed per day and the frequency per week. Excess alcohol intake was defined as alcohol intake of ≥300 g/week, according to the results of the Japan Public Health Center study. The presence of a parental history of hypertension was also determined by a ‘yes’ or ‘no’ question. As described in our previous report, the participants were asked ‘How often do you eat salty foods?’ The possible answers were ‘seldom’, ‘sometimes’ or ‘always’, and the answers were taken as a subjective assessment. To answer the question, the participants were required to decide upon two issues based on their impressions: (i) whether or not the consumed foods were actually salty; and (ii) the frequency with which they consumed salty foods.

**Statistical analysis**

All statistical tests were performed using the SPSS software programme (version 19.0.0, IBM, Somers, NY, USA). Continuous variables with and without a skewed distribution were expressed as the median (interquartile range) and the mean ± standard deviation respectively.
Categorical data were expressed as per cent of the total. The subjects were divided into three groups according to their frequency of salty food intake (i.e. ‘seldom’, ‘sometimes’ and ‘always’ groups) for the subsequent analysis. The baseline characteristics among the groups were compared by an analysis of variance, the Chi-squared test or the Kruskal–Wallis test, as appropriate. The cumulative incidence of hypertension was compared using the Kaplan–Meier method and the log–rank test. A Cox proportional hazards model was used to identify independent predictors for the risk of incident hypertension. All statistical tests were two sided and a $P$-value of $<0.05$ was considered significant.

**Results**

For the entire study population at baseline, the mean age was $44 \pm 6$ years, and the systolic and diastolic BP were $116 \pm 11$ mmHg and $74 \pm 9$ mmHg respectively. The characteristics of the study participants, according to their reported frequency of salty food intake, are shown in Table 1. The number of subjects corresponding to the ‘seldom’ ‘sometimes’ and ‘always’ groups was 179, 662 and 129 respectively. Age, body mass index and the prevalence of excess alcohol intake were significantly different among the groups. There were no significant differences in the systolic or diastolic BP, the proportion of subjects in each BP category, or other variables among the groups.

During a total follow-up period of 3431 person-years (average; 3.5 years), 87 subjects were lost to follow-up and 129 subjects were judged to have developed hypertension (annual incidence rate, 2.54 per 100 person-years). The development of hypertension was seen in 28, 90 and 13 subjects in the ‘seldom’, ‘sometimes’ and ‘always’ groups respectively; the Kaplan–Meier analysis revealed that the 4-year cumulative incidence of hypertension was not significantly different among the groups (15.8%, 14.3% and 10.3% respectively; log–rank, $P = 0.44$).

The results of the Cox proportional hazards model for the risk of incident hypertension are shown in Table 2. In the multi-adjusted model, older age, higher body mass index and higher baseline BP category showed a significantly higher hazard ratio for the risk of incident hypertension. However, the frequency of salty food intake for the ‘sometimes’ or ‘always’ group, relative to the ‘seldom’ group, did not significantly increase or decrease the hazard ratios in the unadjusted, the age- and sex-

**Table 1** Baseline characteristics of the study participants according to the frequency of salty food intake

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency of salty food intake</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Seldom</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Number of participants</td>
<td>179</td>
<td>662</td>
</tr>
<tr>
<td>Age (years)</td>
<td>$45 \pm 6$</td>
<td>$43 \pm 6$</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>165 (92.2)</td>
<td>608 (91.8)</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>$22.6 \pm 2.9$</td>
<td>$22.9 \pm 2.7$</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>$117 \pm 10$</td>
<td>$116 \pm 11$</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>$74 \pm 7$</td>
<td>$74 \pm 8$</td>
</tr>
<tr>
<td>BP category†, n (%)</td>
<td>Optimal</td>
<td>342 (51.7)</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>190 (28.7)</td>
</tr>
<tr>
<td></td>
<td>High-normal</td>
<td>130 (19.6)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>47 (26.3)</td>
<td>183 (27.6)</td>
</tr>
<tr>
<td>Weekly alcohol intake (g/week)</td>
<td>57.5 (11.5, 149.5)</td>
<td>57.5 (11.5, 149.5)</td>
</tr>
<tr>
<td>Excess alcohol intake, n (%)</td>
<td>7 (3.9)</td>
<td>41 (6.2)</td>
</tr>
<tr>
<td>Regular exercise, n (%)</td>
<td>47 (26.3)</td>
<td>138 (20.8)</td>
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<tr>
<td>Family history of hypertension, n (%)</td>
<td>39 (21.8)</td>
<td>160 (24.2)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>$198 \pm 32$</td>
<td>$199 \pm 32$</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>$59 \pm 13$</td>
<td>$57 \pm 14$</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>81 (53, 112)</td>
<td>89 (59.5, 130)</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>61 (34.1)</td>
<td>247 (37.3)</td>
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<tr>
<td>Uric acid (mg/dL)</td>
<td>5.7 (1.2)</td>
<td>5.8 (1.3)</td>
</tr>
<tr>
<td>Hyperuricaemia, n (%)</td>
<td>30 (16.8)</td>
<td>119 (18.0)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>90 (9)</td>
<td>91 (12)</td>
</tr>
<tr>
<td>Impaired fasting glucose/diabetes, n (%)</td>
<td>9 (5.0)</td>
<td>29 (4.4)</td>
</tr>
</tbody>
</table>

†The BP category is in accordance with the 2009 Japanese Society of Hypertension Guidelines for the Management of Hypertension (systolic/diastolic BP of $<120/80$ mmHg, $<130/85$ mmHg and $130–139/85–89$ mmHg as optimal BP, normal BP and high-normal BP categories respectively). BP, blood pressure; HDL, high-density lipoprotein.
adjusted, or the multi-adjusted models. When the multivariate Cox proportional hazards model was used for only the 897 male subjects, the findings were similar to those observed in the analysis that included all the study subjects (data not shown).

**Discussion**

In this 4-year observational study conducted in a middle-aged population, the subjectively evaluated frequency of salty food intake was not associated with the risk of incident hypertension. We previously examined the association between the subjective evaluation of the frequency of salty food intake and actual salt intake among 419 middle-aged workers, using the same questionnaire as in the present study.9 In the study, the confounder-adjusted daily urinary sodium excretion was significantly different among the ‘seldom’, ‘sometimes’ and ‘always’ groups (147 ± 36, 152 ± 36 and 161 ± 36 mEq/day respectively, \( P = 0.049 \)); in addition, the prevalence of high salt intake, defined as higher than average Japanese daily salt intake (≥11.5 g/day for men and ≥9.9 g/day for women) according to the National Health and Nutrition Survey in 2010,12 gradually increased across the ‘seldom’, ‘sometimes’ and ‘always’ groups (10.3%, 13.4% and 24.0% respectively, \( P = 0.013 \) for trend). These observations suggest that the information obtained from this questionnaire on the frequency of salty food intake may reflect actual salt intake. However, a relationship between such subjective information and BP was not observed in that study, possibly because of its cross-sectional study design. Therefore, we had hypothesised that a subjective evaluation of the frequency of salty food intake could predict the future development of hypertension through a longitudinal study. However, unexpectedly, the present 4-year follow-up study once again failed to verify the hypothesis.

There are several possible explanations for the present findings. First, the degree of BP elevation induced by salt loading in each individual, which is known as salt sensitivity,13 was not elucidated in the present study. The heterogeneity of this study population with respect to salt sensitivity may have affected the present results. Second, the present analysis did not consider any changes in the habits of salty food intake during the follow-up period. In particular, subjects in the ‘always’ group at baseline may have attempted to abstain from salty food, thus resulting in a biasing of the present results towards the null hypothesis. In addition, the maximum follow-up period of 4 years may have been insufficient to obtain statistically significant results in this study population.

The predictors for the development of hypertension in the present study were age, body mass index and the baseline BP category. These results are in line with the previous observations.14,15 In contrast, the present study did not show any significant association between the risk of incident hypertension and parental history of hypertension, smoking status, alcohol intake, exercise habits or uric acid levels, all of which have previously been reported to predict the future development of hypertension.16–24 A longer follow-up period may be needed to elucidate such associations in this study population.

Table 2  Cox proportional hazards model for the risk of incident hypertension

<table>
<thead>
<tr>
<th>Explanatory variables</th>
<th>Unadjusted</th>
<th>Age- and sex-adjusted</th>
<th>Multi-adjusted</th>
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<tr>
<td></td>
<td>HR 95% CI</td>
<td>P-value</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Frequency of salty food intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seldom</td>
<td>1.00</td>
<td>Reference</td>
<td>1.00</td>
</tr>
<tr>
<td>Sometimes</td>
<td>0.89</td>
<td>0.58–1.38</td>
<td>0.45</td>
</tr>
<tr>
<td>Always</td>
<td>0.65</td>
<td>0.34–1.27</td>
<td>0.21</td>
</tr>
<tr>
<td>Age (per 1-year increase)</td>
<td></td>
<td></td>
<td>1.07</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td>1.23</td>
</tr>
<tr>
<td>Body mass index (per 1 kg/m² increase)</td>
<td></td>
<td></td>
<td>1.08</td>
</tr>
<tr>
<td>BP category† (per 1-category increase)</td>
<td></td>
<td></td>
<td>3.12</td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Regular exercise</td>
<td></td>
<td></td>
<td>1.25</td>
</tr>
<tr>
<td>Excess alcohol intake</td>
<td></td>
<td></td>
<td>1.46</td>
</tr>
<tr>
<td>Parental history of hypertension</td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td></td>
<td></td>
<td>1.18</td>
</tr>
<tr>
<td>Impaired fasting glucose/diabetes</td>
<td></td>
<td></td>
<td>1.42</td>
</tr>
</tbody>
</table>

†The BP category is in accordance with the 2009 Japanese Society of Hypertension Guidelines for the Management of Hypertension (systolic/diastolic BP of <120/80 mmHg, <130/85 mmHg, and 130–139/85–89 mmHg as optimal BP, normal BP, and high-normal BP categories respectively). BP, blood pressure; CI, confidence interval; HR, hazards ratio.
The present study has several limitations. First, although several potential confounders were examined in the present multivariate analysis, other confounders that could not be tested in this study, such as socioeconomic factors, may have affected the results. Second, as noted above, possible lifestyle changes of the study participants during the follow-up period could not be taken into consideration. Third, whether the subjective evaluation of the frequency of salty food intake accurately reflects actual salt intake was not examined in the present study. However, as mentioned above, the relationship has been validated in our previous study that included subjects with clinical characteristics similar to those in the present study. Finally, the study participants included only middle-aged, Japanese workers at a single manufacturing facility. Therefore, whether the present results can be extrapolated to other populations, including the elderly or different ethnic groups, is unclear.

**Conclusion**

The present study did not show any significant association between the subjective evaluation of the frequency of salty food intake and the risk of incident hypertension during a 4-year period. These results suggest that this information is of low utility for identifying subjects at high risk for incident hypertension. Further investigations with a longer follow-up period are expected to clarify whether the present results are valid beyond a 4-year period.

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Salty food intake and hypertension risk

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Key words
time and motion, night-shift, work practice, junior doctor.

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Abstract
Background: It is imperative to understand the current work practices of hospital personnel to inform efforts and secure resources towards the improvement of hospital systems. Research examining doctors’ work during night-shifts is limited.
Aim: To describe and quantify the night-shift work practices of junior doctors.
Methods: An observational time and motion study was conducted. Eight resident doctors in four general wards were observed for 96 h during night shifts (Monday–Friday, 2200–0800).
Results: Doctors spent the highest proportion (28%; 95% CI 21–35) of their time performing social/personal tasks (e.g. sleeping, eating) and indirect care (24%; 95% CI 22–25) (e.g. reviewing notes, ordering tests). Work-related discussion comprised 15% (95% CI 13–17), and most took place at the beginning of the night. Medication-related tasks consumed a small proportion of time (4%; 95% CI 3–4) but attracted a higher level of multitasking and interruptions than most other tasks. On average, 2 h of every shift were spent at a computer and 1.3 h with patient notes. Doctors spent 72% of the night-shift alone, multitasked 6.4% of the time and were interrupted, on average, once every 46 min.
Conclusions: This study provides new data about junior doctors’ work at night. Relative to doctors during the day, greater proportions of time were devoted to social/personal tasks (including sleep) and indirect care, but a similar proportion to direct care. Multitasking and interruptions were minimal. Computer activities were an integral part of work. Handovers were observed at the beginning but not the completion of the night shift, which may have implications for patient safety.

Introduction
The nature of healthcare delivery has always been complex and dynamic, but in recent years, healthcare systems have been inundated with additional challenges. Hospital admissions are on the rise,1,2 and the burden of chronic illness associated with an ageing population is increasing.3 Technological innovations aimed at improving the quality, safety and efficiency of patient care have added a new layer of complexity to clinical work. Moreover, the recent adoption of an Activity Based Funding model in Australia is associated with major changes and potential challenges in the organisation, funding and delivery of healthcare.4 Improving workforce

productivity without compromising patient safety is a fundamental step in overcoming these growing challenges. It is imperative first to understand the current work practices of hospital personnel to inform efforts and secure resources towards the improvement of hospital systems.

Although some quantitative studies of doctors’ and nurses’ work practices have begun to emerge,6–8 research examining doctors’ work during night shifts is very limited. It is primarily junior doctors who oversee the medical care of patients in general wards at night, with fewer doctors to manage patients than during the day. Research has shown that night-shift workers have impaired performance compared to day-shift workers,8 that errors in hospitals occur more frequently at night,9,10 and there is some evidence to suggest that hospitalised patients receive poorer quality of care at night than during the day.11,12 However, few studies have examined what junior doctors on general wards do during the night shift. Much of the literature exploring night-time work is outdated and suffers from significant methodological limitations, such as reliance on self-report to collect data, and failures to collect or report important information (e.g. task durations13,14 or task definitions15–17). A quantitative examination of doctors’ work practices is needed to understand more fully junior doctors’ night-shift work, including what tasks they perform, when they perform them and for how long. These baseline data are not only valuable for examining any changes in work practices that may occur following hospital system interventions but also can dispel or confirm assumptions about the work of junior doctors at night. We conducted a time-and-motion study to identify and describe the work practices of junior doctors on weekday night shifts.

Methods

Setting and sample

The study was conducted in the general wards of a 330-bed tertiary teaching hospital in Sydney, Australia. Paper clinical notes are used on all general wards, while tasks, such as ordering tests and medications, viewing results and ordering consultations and patient transportation are conducted using a computerised provider order entry system. Wards (typically 34 beds) vary in the number of computers available, but all are equipped with on average eight wireless laptops fixed to lightweight trolleys and eight desktop computers located at clinical work stations. At night, patients’ medical care is generally overseen by one surgical and one medical resident medical officer (RMO) with registrars working in the Emergency Department available in emergency situations. Of the 10 RMO working night shifts during the study period (May–July, 2012), eight agreed to participate in our study. Resident doctors were observed on weekdays between 22:00 and 08:00 for a total of 96 h, with equal coverage of each weekend and times.

Data collection tool

The Work Observation Method by Activity Timing (WOMBAT; Sydney, NSW, Australia) software, running on a portable touch screen tablet was used to collect data. WOMBAT is time-and-motion software designed to capture the complex working patterns of clinicians in real time.16,17 A multidimensional work task classification system based on doctors’ day-shift work practices was devised to categorise doctors’ practices at night.18 After several night-shift pilot sessions, the classification was refined (Table 1) and incorporated into the WOMBAT application. The final classification had 11 mutually exclusive work tasks, and recorded tasks were automatically time stamped. The tool allowed for the multiselectable classification for some tasks, e.g. whom the doctor interacted with (e.g. nurse, patient) and what tools the doctor used (e.g. desktop computer, phone) for each task. Any interruptions to work or multitasking events that occurred were recorded. Observed activities were classified as a new task when any of the variables of interest changed, that is, the task being carried out, the people present or the tools being used.

Procedure

Resident doctors were shadowed by an observer (PA) for two or three 120-min session per night, with 120-min break between sessions and observed for up to a total of three night shifts. The observer recorded all information using the tablet computer. Ethics approval was obtained from the Human Research Ethics Committee of the hospital and the University of New South Wales.

Statistical analysis

Descriptive statistics with 95% confidence intervals (CI) were calculated to identify the proportion of time spent in various tasks, levels of multitasking and the rate of interruptions. The time on task was summarised by the median due to skewness, with distribution free 95% CI.18 CI for the proportion of total time and the proportion of time spent multitasking assume a normal distribution. This can generate lower limits beyond the plausible range. Where this is the case, the lower limit is recorded as zero. CI for interruptions were calculated by Poisson regression with task type as the only categorical covariate.
No differences in the work practices or rates of multitasking and interruptions were observed for surgical and medical junior doctors so data for the two groups were combined for the analysis.

**Results**

During the 96 h of observation, a total of 6148 distinct tasks were observed which amounted to a total task time of 102.4 h. Disparity between observed versus total time is due to simultaneous task performance (multitasking). On average, doctors spent 6.4% of their time on the night-shift multitasking. Task durations ranged from one second (quick documentation, e.g. a signature) to more than 2 h (e.g. sleeping, recorded as ‘personal/social’), with a median task duration of 25 s. The task-specific distribution of doctors’ time is shown in Table 2.

Over a quarter of the total night-shift observation time was spent in personal/social activities, including sleeping, eating, resting and other non-work-related tasks. The number of personal/social tasks performed was relatively small compared with other tasks, but social tasks had a relatively long average duration, primarily due to periods of sleep (Table 2). The pattern of activity across a standard night shift is illustrated in Figure 1. This shows a high proportion of time spent on work tasks at the beginning of the shift with a steady increase in personal/social activity, peaking around 4–6 am when many doctors were able to gain some sleep.

Indirect care consumed the second highest proportion of time (24%). 4.3% of which was spent searching, 8.6% organising equipment and the remaining 87.0% on other tasks, such as reviewing patient information. Collectively, the number of indirect care tasks accounted for almost a third of all tasks, with a median duration of 26 s. Of the

<table>
<thead>
<tr>
<th>Table 1 Work classification of doctors’ night-shift practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work task</td>
</tr>
<tr>
<td>Direct care</td>
</tr>
<tr>
<td>Indirect care</td>
</tr>
<tr>
<td>Search</td>
</tr>
<tr>
<td>Equipment</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Professional communication</td>
</tr>
<tr>
<td>Documentation</td>
</tr>
<tr>
<td>Medication</td>
</tr>
<tr>
<td>Transcribe</td>
</tr>
<tr>
<td>Other medication tasks</td>
</tr>
<tr>
<td>Social/Personal</td>
</tr>
<tr>
<td>In transit</td>
</tr>
<tr>
<td>Pager†</td>
</tr>
<tr>
<td>Administration</td>
</tr>
<tr>
<td>Supervision/Education</td>
</tr>
<tr>
<td>Waiting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>With whom</th>
<th>With what</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Laptop computer</td>
</tr>
<tr>
<td>Nurse</td>
<td>Desk-PC</td>
</tr>
<tr>
<td>Allied health</td>
<td>Smart phone</td>
</tr>
<tr>
<td>Specialist</td>
<td>Patient notes</td>
</tr>
<tr>
<td>Registrar</td>
<td>Paper</td>
</tr>
<tr>
<td>Junior doctor</td>
<td>Telephone</td>
</tr>
<tr>
<td>Relative</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td></td>
</tr>
<tr>
<td>Administrative</td>
<td></td>
</tr>
</tbody>
</table>

†Pager is always entered as an interruption. When tasks are completed simultaneously they are recorded as a ‘multitask’. Any new task that results in the cessation of a current task is recorded as an ‘interruption’.

| Table 2 Doctors’ work activities during the night-shift (Monday–Friday, 2200–0800) |
|---------------------------------|-------------------|-----------------|-------------------|-----------------|-------------------|-------------------|-------------------|
| Task type | N tasks | Time on task (s) | Proportion of total task time | Multitasking time | Interruption rate per hour |
| | | Median | 95% CI | % | 95% CI | % | 95% CI | Rate | 95% CI |
| Social/Personal | 418 | 52 | 41, 65 | 27.6 | 20.5, 34.8 | 2.3 | 0.4, 7.1 | 0.6 | 0.4, 1.0 |
| Indirect care | 1913 | 26 | 25, 28 | 23.7 | 22.4, 25.0 | 17.8 | 13.5, 22.1 | 1.5 | 0.5, 4.3 |
| Professional communication | 1092 | 26 | 23, 28 | 15.4 | 13.4, 17.4 | 33.2 | 27.1, 39.3 | 1.4 | 0.5, 4.3 |
| Direct care | 356 | 82 | 68, 95 | 13.0 | 11.6, 14.5 | 0.5 | 0.1, 10.8 | 0.8 | 0.2, 2.8 |
| In transit | 1257 | 14 | 13, 15 | 11.0 | 10.2, 11.9 | 3.4 | 1.3, 5.4 | 1.0 | |
| Documentation | 641 | 24 | 22, 26 | 7.3 | 6.6, 8.0 | 18.7 | 15.5, 25.9 | 2.6 | 0.8, 8.0 |
| Other† | 184 | 30 | 23, 36 | 4.2 | 2.9, 5.5 | 5.9 | 0.20.5 | 1.0 | 0.2, 4.7 |
| Medication | 202 | 45 | 38, 50 | 3.7 | 3.2, 4.2 | 18.7 | 6.8, 30.6 | 2.6 | 0.7, 9.2 |
| Pager | 85 | 10 | 8, 11 | 0.3 | 0.3, 0.3 | 10.5 | 0.22, 35.2 | 3.6 | 0.3, 43.3 |
| Overall | 6148 | 25 | 24, 26 | | | | |

†Other consists of supervision/education (2.3%), waiting (1.3%) and administrative (0.6%). ‡95% CI for the median are distribution free. CI, confidence interval.
total time spent in indirect care, half was spent using a computer and almost a third reviewing patient notes. More than 95% of computer tasks were completed using a desktop computer, with very little use of laptop computers observed (Table 3).

The third highest proportion of time on night shifts was spent in professional communication. The most communication occurred at the beginning of the shift (Fig. 1). About half of the communication observed was with nurses, and approximately a third with other junior doctors (Table 3). The highest rate of multitasking occurred during professional communication (33% of all these tasks involved multitasking) (Table 2). Junior doctors spent the majority (72%) of time alone, with less than 3 h of each 10-h shift spent with other people (including patients).

Direct care consumed a relatively low proportion of time (13.0%), but these tasks had the longest median duration. On average, 43.8 min per 10-h shift were spent documenting. Documenting on a computer accounted for only 10% of the total documentation time, over twice this proportion was spent writing on scraps of paper, while the majority of documentation involved writing in patient files. During documentation and also medication-related tasks, doctors spent more time multitasking and were interrupted more frequently compared to most

Table 3  With whom, and with what tools, doctors spent their time during the night-shift (Monday–Friday, 2200–0800)

<table>
<thead>
<tr>
<th>With whom</th>
<th>N tasks</th>
<th>Time on task</th>
<th>Proportion of total task time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (s)</td>
<td>95% CI†</td>
<td>% 95% CI</td>
</tr>
<tr>
<td>No one</td>
<td>4223</td>
<td>22</td>
<td>21, 23</td>
</tr>
<tr>
<td>Nurse</td>
<td>1135</td>
<td>27</td>
<td>24, 30</td>
</tr>
<tr>
<td>Patient</td>
<td>370</td>
<td>76.5</td>
<td>66, 94</td>
</tr>
<tr>
<td>Junior doctor</td>
<td>470</td>
<td>37</td>
<td>33, 41</td>
</tr>
<tr>
<td>Registrar</td>
<td>281</td>
<td>37</td>
<td>30, 46</td>
</tr>
<tr>
<td>Specialist</td>
<td>30</td>
<td>30</td>
<td>15, 93</td>
</tr>
<tr>
<td>Admin</td>
<td>36</td>
<td>29.5</td>
<td>19, 45</td>
</tr>
<tr>
<td>Allied Health</td>
<td>8</td>
<td>15</td>
<td>13, 170</td>
</tr>
<tr>
<td>Relative</td>
<td>2</td>
<td>25</td>
<td>19, 32</td>
</tr>
<tr>
<td>Student</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>With what</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desk PC</td>
<td>980</td>
<td>41.0</td>
<td>37, 44</td>
</tr>
<tr>
<td>Patient record</td>
<td>988</td>
<td>30.0</td>
<td>27, 23</td>
</tr>
<tr>
<td>Telephone</td>
<td>128</td>
<td>42.0</td>
<td>35, 51</td>
</tr>
<tr>
<td>Paper</td>
<td>338</td>
<td>14.0</td>
<td>13, 16</td>
</tr>
<tr>
<td>COW</td>
<td>51</td>
<td>37.0</td>
<td>29, 54</td>
</tr>
<tr>
<td>Smart phone</td>
<td>44</td>
<td>41.0</td>
<td>22, 66</td>
</tr>
</tbody>
</table>

†95% CI for the median are distribution free. COW, computer on wheels.
other tasks (Table 2). Medication-related tasks consumed a very small proportion of time, and 23% of all medication time was spent transcribing medications from paper (i.e. orders generated in the emergency department where no electronic medication ordering system was available) to the electronic medication system used on all general wards. During the night shift, doctors also spent on average 66 min in transit.

**Interruptions**

A total of 125 interruptions was seen during the observation period, a rate of 1.3 interruptions per hour. The most frequent source of interruptions was pagers (68%, \( n = 84 \)) followed by colleagues and other professionals (32%, \( n = 40 \)). Pager interruptions were highly variable and occurred 0–11 times per night (median = 3.5).

**Discussion**

During weekday night shifts between 10:00 pm and 8:00 am, we found that junior doctors spent the majority of their time alone and distributed half their time between personal activities (predominantly sleeping), which made up around 2.7 h per shift, and indirect care tasks which consumed 2.4 h per shift. A further 15% (1.5 h) of their task time was devoted to communication about patient care, and a further 13% was spent in direct care.

Indirect care consumed almost a quarter of doctors’ time. During the piloting stage, several doctors expressed frustration and argued that they spent their ‘whole shift preparing equipment for a procedure’ (e.g. gathering the components required to insert a cannula) or searching for objects (e.g. misplaced patient files) and described this as a ‘waste of time’. Direct observation revealed that doctors spent on average 6 min per shift searching and 12 min performing equipment-related tasks. Doctors and nurses observed during the day shift in previous studies have also complained of wasting a lot of time in activities which, when measured, actually consumed a very small proportion of their time.\(^1\) Time-and-motion studies provide us with quantitative data to feedback to staff to change perceptions of the time spent on these tedious but essential tasks.

Doctors spent approximately 92 min per shift engaged in professional communication, and a large proportion of this took place at the start of the shift during handover. Patient handover is recognised as a critical step in providing safe and quality patient care and in recent years, optimising handover and the prevention of errors related to poor handover has been the focus of several patient safety initiatives.\(^{19–21}\) Despite this, no official exchange was observed at the end of any of the night shifts observed at our study site. The absence of morning handover has also been reported at several other Australian hospitals\(^22\) and contradicts Australian Medical Association patient handover guidelines.\(^19\) The absence of effective handover processes in the morning may place patients at increased risk of errors. Junior doctors spent the vast majority of time working alone and worked with registrars for an average of 1 h per shift.

This is the first study identified to quantify the amount of time doctors spend engaging in direct care at night. We found that doctors spent approximately 13% of their night shift in direct care, a proportion comparable to the proportion observed during the day (15%).\(^1\) In contrast, the proportion of time that doctors spent in transit at night (11%) was almost double that recorded during the day (6%).\(^1\) This is most likely a consequence of having fewer doctors monitoring the same number of patients at night who are located across the hospital. We also found that medication-related tasks consumed almost half the time at night than they did during the day.\(^1\) Although the overall levels of multitasking and interruption experienced by night-shift junior doctors were considerably lower than during the day,\(^1\) their higher occurrence during medication tasks in particular may contribute to increased risk of error.\(^21\)

We observed heavy usage of hospital information technology at night, with approximately 113 min (19% of their time) of every night shift spent at a computer. The majority of computer tasks was performed on desktop computers, rather than laptops. There was also very little use of smartphones. Although smartphones provide easy access to information and reference sources, doctors are not currently able to access hospital clinical information systems on their smartphones.

**Limitations**

Although participants may have changed their behaviour due to being observed, the magnitude of this effect is likely to be minimal, given that no assessment of quality was being made by the observer and external factors largely dictated their work. We were only able to observe eight participants, but they represented 80% of all junior doctors rostered on to after-hour shifts during this two-month period. The present study examined junior doctors’ weeknight practices, and these may not be representative of tasks performed on the weekend after-hour shift. The study was also only conducted at one hospital, and so these baseline data may not be representative of other sites where night-time staffing is different. Although direct statistical (inter-experiment) comparisons cannot be made between night and day work practices, these findings do allow general trends to be identified.
Conclusion

To our knowledge, this is the first study to quantify the tasks junior doctors perform at night, including with whom, with what tools and rates of multitasking and interruptions. Doctors working the night shift appeared to have time to rest with few interruptions to work and low levels of multitasking. Although handover was observed at the start of the shift, no morning handover took place. Patient notes and computers both appeared to be an integral part of patient care. A small proportion of the night shift was spent completing medication tasks, but doctors experienced the most interruptions during these tasks. This study provides baseline data which will allow us to monitor and assess the impact of future changes and interventions affecting doctors’ night-shift work, ultimately facilitating the improvement of care delivery.

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BRIEF COMMUNICATIONS

Indian-born patients attending a sexual health clinic in Australia have differing characteristics to their Australian-born counterparts

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Key words
sexual health, migrant, CALD population, STI, health promotion.

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Abstract
We report a retrospective cross-sectional study from Western Sydney that assessed the sexual health characteristics of Indian-born patients attending sexual health services compared with Australian-born controls. The sexual health needs of Indian-born patients differed significantly from controls with those born in India reporting more sexual dysfunction and controls having more sexually transmitted infections (STI). These issues should be considered when delivering services to people from culturally and linguistically diverse backgrounds.

The cultural diversity of Australia’s population has increased markedly in the past 20 years, with a broadening of source countries for migration,1 and an increase in the number of people coming from countries with higher prevalence rates of human immunodeficiency virus (HIV) compared with Australia.2 Data indicate that in 2007–2008, Indian-born people formed the third largest migrant group, after the United Kingdom (UK) and New Zealand.3

Migrants and people belonging to culturally and linguistically diverse (CALD) background groups are often at risk of poor health outcomes, especially in relation to sexual health.4–7 For example in the UK, people from the Indian subcontinent were significantly different from people of English origin in terms of their sexual behaviour and contraceptive use.8

There are a few published studies regarding the sexual health of CALD communities in Australia,9,9.10 but none from Indian-born patients attending a sexual health clinic (SHC), and this led us to investigate whether there were any significant differences between Indian-born and Australian-born counterparts attending our SHC in Western Sydney.

A retrospective cross-sectional study was conducted at the Parramatta Sexual Health Clinic (PSHC), one of four publicly funded SHC in Western Sydney.

Cases were Indian-born patients whereas gender-matched controls were attendees born in Australia who attended PSHC between the same time period namely, 1 January 2007 and 1 January 2009.

All those known to be infected with HIV were excluded from the analysis, as the study focused on sexual health issues.

Data recorded included demographics, sexual practices, sexually transmitted infections (STI) and the use of other clinic services such as interpreters, social workers or clinical psychologists.

Data were analysed using SPSS Version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Groups were compared for differences. Pearson’s Chi-squared (or the Fisher’s exact) test were used to compare proportions in $2 \times 2$ tables. Means were compared using independent samples $t$-test. The study was approved by the Sydney West Area Health Service Human Research Ethics Committee.

Of the 166 records for Indian-born patients available for analysis, 123 (74%) were males and 43 (26%) were females. The median age of cases was significantly lower (29 years, range 17–58 years) compared with controls.
(39 years, range 21–75 years). Of the 101 Indian-born patients for whom information regarding English language was recorded, only nine (9%) reported that they did not speak English at home; however, only one person requested an interpreter.

Table 1 summarises the reasons for attendance, the main diagnosis and the use of services by Indian-born patients and Australian-born controls. Indian-born patients were significantly more likely to have attended because of sexual dysfunction than controls (15.7% vs 1.8%; \( P < 0.001 \)); however, controls were more likely to have attended for STI screening than Indian-born patients (36.1% vs 24.7%; \( P = 0.032 \)). Similar differences were noted in the main diagnosis recorded by the healthcare provider. Indian-born patients (12.7%) were significantly more likely to use the services of the clinical psychologist compared with controls (4.2%).

Of the 139 Indian-born patients in whom partner status was recorded, 94 (67.7%) reported a regular partner. This was a similar percentage to controls, of whom 99 (67.3%) reported regular partners. Same sex regular partner was reported by four (4.2%) in the Indian-born group compared with 16 (16.1%) of controls (\( P = 0.04 \)).

Information about condoms use and visit to sex worker was incomplete.

A total of 227 symptoms was reported from Indian-born patients and Australian-born patients. That is, 85 (51.2%) Indian-born patients reported 129 (56.8%) of the total of 227 anogenital symptoms, including 26 sexual dysfunction-related complaints. In contrast, 86 (51.8%) controls reported 98 (43.2%) of the total anogenital symptoms, including only three sexual dysfunction-related complaints. Of 26 Indian-born patients who presented with symptoms related to sexual dysfunction, 21 had a sexual dysfunction diagnosis confirmed by the healthcare provider. This included 10 patients with premature ejaculation, six patients with erectile dysfunction and five with various other sexual dysfunction issues. Sexual dysfunction was significantly more likely to be reported by Indian-born patients (\( P = 0.001 \)) compared with Australian-born controls.

There were no other significant differences between the groups in reported anogenital symptoms.

A total of 77 STI diagnoses and reproductive tract infections diagnoses were made in 75 patients, 30 (18.1%) in Indian-born patients and 47 (28.3%) in controls. Table 2 shows STI diagnosed at the study visit. Controls were significantly more likely to be diagnosed with STI compared with Indian-born patients, although there were similarities in the spectrum of STI diagnosed in both groups. The most common STI diagnosed at the study visit in each group was genital warts, followed by herpes simplex virus and chlamydia.

We found significant differences in reasons for attendance, anogenital symptoms and STI diagnoses between Indian-born patients and Australian-born patients presenting to our SHC.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Indian born (n = 166)</th>
<th>Australian born (n = 166)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for attendance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STI screening</td>
<td>41 (24.7%)</td>
<td>60 (36.1%)</td>
<td>0.0318</td>
</tr>
<tr>
<td>Anogenital symptoms</td>
<td>73 (44%)</td>
<td>88 (53%)</td>
<td>0.1242</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>26 (15.7%)</td>
<td>3 (1.8%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Others</td>
<td>23 (13.8%)</td>
<td>13 (8%)</td>
<td>0.1122</td>
</tr>
<tr>
<td>Not known</td>
<td>3 (1.8%)</td>
<td>2 (1.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Main diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic STI screening</td>
<td>52 (31.3%)</td>
<td>80 (48.2%)</td>
<td>0.002</td>
</tr>
<tr>
<td>STI/RTI</td>
<td>30 (18%)</td>
<td>47 (28.3%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>21 (12.6%)</td>
<td>4 (2.4%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Others†</td>
<td>49 (29.5%)</td>
<td>32 (19.3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Not recorded</td>
<td>14 (8.4%)</td>
<td>3 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Condom use in the past 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number where recorded</td>
<td>96</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>23 (23.9%)</td>
<td>34 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>38 (39.6%)</td>
<td>31 (26%)</td>
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</tr>
<tr>
<td>Sometimes/50%</td>
<td>34 (35.4%)</td>
<td>51 (42.8%)</td>
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</tr>
<tr>
<td>Not applicable</td>
<td>1 (1%)</td>
<td>3 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Use of interpreter services</td>
<td>1 (0.6%)</td>
<td>0 (0%)</td>
<td></td>
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<tr>
<td>Use of social worker services</td>
<td>7 (4.2%)</td>
<td>10 (6%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Use of clinical psychologist services</td>
<td>21 (12.7%)</td>
<td>7 (4.2%)</td>
<td>0.009</td>
</tr>
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</table>

†Others included information, vaccination, genital dermatological and other non-STI-related conditions. RTI, reproductive tract infections; STI, sexually transmitted infection.
Concerns. A ‘SHC’ may therefore be perceived as a specialist centre for all concerns. Of 26 Indian-born patients who presented with symptoms related to sexual dysfunction, 21 had the sexual dysfunction diagnosis confirmed by the healthcare provider. This is consistent with literature from India regarding sexual dysfunction, where patients may perceive their problems as sexual dysfunction but may actually be related to ‘loss of semen’, ‘penis size’, ‘masturbation’, etc. It is thus possible that cultural expectations of sexual function may significantly impact on presenting behaviour to SHC. Most common sexual dysfunction diagnosis reported in our study was premature ejaculation, which is consistent with studies in the CALD population. A ‘SHC’ may therefore be perceived as a specialist centre for all concerns. Of 26 Indian-born patients who presented with symptoms related to sexual dysfunction, 21 had the sexual dysfunction diagnosis confirmed by the healthcare provider. This is consistent with literature from India regarding sexual dysfunction, where patients may perceive their problems as sexual dysfunction but may actually be related to ‘loss of semen’, ‘penis size’, ‘masturbation’, etc. It is thus possible that cultural expectations of sexual function may significantly impact on presenting behaviour to SHC. Most common sexual dysfunction diagnosis reported in our study was premature ejaculation, which is consistent with studies in the CALD population.

**References**


Distal renal tubular acidosis associated with Sjogren syndrome

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Key words
renal tubular acidosis, hypokalaemia, urine anion gap, urine osmolal gap, transtubular potassium gradient, Sjogren’s syndrome.

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Abstract
Renal tubular acidosis is a common cause of normal anion gap metabolic acidosis but these disorders can be easily missed or misdiagnosed. We highlight the approach to assessing renal tubular acidosis by discussing a case study with a temporal data set collected over more than 5 weeks. We highlight the principles and the necessary information required for a diagnosis of classic distal renal tubular acidosis. We also briefly review several aspects of type 1 renal tubular acidosis related to autoimmune disease, drugs and thyroid disorders.

Renal tubular acidosis (RTA) may cause normal anion gap (hyperchloaemic) metabolic acidosis. We discuss the approach to RTA, principles of investigation and briefly review the association of type 1 RTA with autoimmune disease, drugs and thyroid disorders.
A 69-year-old woman collapsed at home with profound weakness. Her medical history included hypothyroidism, osteoarthritis, polymyalgia rheumatica and fatty liver. Her medications were thyroxine 100 mcg and amitriptyline 50 mg daily. She had noted 1 week of increasing weakness, with proximal limb aches and pains. Her doctor prescribed celecoxib 200 mg b.i.d. 4 days prior to presentation. Her symptoms worsened, and she was commenced on prednisolone 50 mg daily the day before presentation. No gastrointestinal symptoms were reported.

On arrival, she was hypothermic (33.1°C) and normotensive (125/70). Arterial blood gas showed mixed metabolic and respiratory acidosis: pH 6.94, PaO2 49 mmHg. PaCO2 68 mmHg, HCO3− 15 mmol/L, base excess −16, lactate 1.6 mmol/L. Serum biochemistry demonstrated: Na+ 138 mmol/L, K+ 1.2 mmol/L, Cl− 115 mmol/L, urea 9.7 mmol/L, creatinine 974 μmol/L, Ca2+ 2.16 mmol/L, PO4− 1.14 mmol/L, Mg2+ 1.25 mmol/L, glucose 18.3 mmol/L and albumin 35 g/L. Serum anion gap was 11 mmol/L. Thyroid function tests 4 days earlier showed adequate replacement: thyroid stimulating hormone 2.99 mU/L (reference range (RR), 0.50–4.00), fT3 14.5 pmol/L (RR, 10.0–19.0), fT4 3.3 pmol/L (RR, 3.5–6.5).

She had flaccid paralysis, and electrocardiogram showed sinus bradycardia, flattened T waves, U waves, first degree heart block and QTc of 492 ms. She was intubated and commenced on a KCl infusion. She remained haemodynamically stable with urine output >50 mL/h. In the first 48 h, blood glucose was regulated by insulin infusion, and empirical ceftriaxone and metronidazole were given. Serum and urine ketones were not elevated. Urine and blood cultures remained sterile.

The first 48 h also saw her serum HCO3− fall to 8 mmol/L and serum Cl− rise to 131 mmol/L. During this time, she received intravascular volume expansion with 0.9% NaCl with 500 mmol of KCl replacement. A robust respiratory compensation, resulting in PaCO2 values of 18–20 mmHg, prevented a fall in arterial pH. HCO3− replacement was initiated, with 500 mmol given intravenously as 0.9% NaHCO3 over 30–40 h. This resulted in normalisation of blood pH, PaCO2, HCO3−, Cl− and K+.

RTA was suggested by the normal anion gap and urine pH >6.0, in addition to a urine K+ (Uk+) >35 mmol/L despite hypokalaemia. Features of proximal tubular dysfunction were absent, including lack of glycosuria (Uglucose < 0.6 mmol/L), aminoaciduria, uricosuria and phosphaturia. Urine protein-creatinine ratio was 0.03 g/mmol (RR, <0.03) with bland urine sediment. Prednisolone and celecoxib were ceased on admission.

Autoimmune studies were positive for anti-nuclear (1:640), anti-Ro, anti-La and anti-TRIM21 antibodies. Anti-neutrophil cytoplasmic antibody, anti-double stranded DNA and anti-cyclic citrullinated peptide were absent, and serum complement was normal. Erythrocyte sedimentation rate was elevated at 60 mm/h (RR, 0–25). On further questioning, the patient had noted dry eyes and mouth for several months, and she was subsequently diagnosed with Sjogren syndrome by two independent rheumatologists. To investigate suspected RTA, K+ and HCO3− supplements were ceased. Baseline blood and urine studies were taken, with daily tests for the next 6 days and subsequently twice weekly on discharge. Figure 1A charts the blood pH, with corresponding urine pH, urine anion gap (UAG) and urine osmolal gap (UOG). Figure 1B charts the serum HCO3− and Cl−.

Figure 2 charts the serum K+, corresponding Uk+ and transtubular K+ gradient (TTKG).

A fall in blood pH, HCO3− and K+ developed after an initial 6 days of stability without supplements. There was a concurrent rise in serum Cl−, and the anion gap remained normal. Acidosis worsened over 2 weeks, while venous PCO2 was 48 ± 5 mmHg (RR, 41–51). Despite progressive acidosis, urine pH remained >7.0, and the UAG remained positive. UOG was consistently <30 mmol/L. Similarly, Uk+ remained high despite falling serum K+, with TTKG values around 10. Recommencement of NaHCO3 and KCl supplements (30–40 mmol/day) corrected the acidosis.

Most causes of normal anion gap (hyperchloraemic) metabolic acidosis result from either a loss of HCO3− from the gastrointestinal tract (e.g. diarrhoea) or kidney (proximal, type 2 RTA), or a defect in net acid excretion in the kidney (distal, type 1 or 4 RTA). Concurrent dyskalaemia is common with these disorders. In order to distinguish between them, it is useful to assess whether the renal response to the acidosis or dyskalaemia is appropriate (non-renal cause) or inappropriate (renal cause). There are several ways to achieve this: (i) assessment of urine pH, (ii) assessment of urine NH4+, (iii) acid-loading test and (iv) assessment of K+ excretion.

Proximal RTA occurs when tubular reclamation of filtered HCO3− is impaired, leading to bicarbonaturia. However, in steady state, the urine is often acidic (pH < 5.5). As serum HCO3− falls, filtered HCO3− declines concurrently to a point where distal HCO3− delivery is normalised. Here, the urine pH is low because distal acidification is intact. Alkali therapy to raise serum HCO3− re-establishes bicarbonaturia, and the urine pH becomes alkaline. HCO3− wasting can be quantified by the fractional excretion of HCO3−, which often exceeds 15–20% following HCO3− infusion. However, urine HCO3− measurement is not validated in all laboratories. A finding of Fanconi syndrome supports the diagnosis of proximal RTA: phosphaturia, uricosuria, glycosuria, aminoaciduria, citraturia, calciuria. Distal RTA (type 1 or 4) occurs...
with a defect in net acid excretion leading to an inability to acidify the urine during acidosis (pH > 5.5). A urine pH < 5.5 makes distal RTA unlikely.

There are limitations in using the urine pH alone for a diagnosis of RTA. As noted, patients with proximal RTA may have variable urine pH depending on whether they have achieved steady state or receiving alkali treatment. Hypokalaemia from gastrointestinal loss can also raise urine pH by stimulating renal ammonia production, which binds luminal H⁺, misleading one to diagnose distal RTA. Finally, infection with urea splitting organisms may raise urine pH by forming ammonia and HCO₃⁻.

In our patient, the inability to acidify urine during acidosis in the absence of alkali treatment suggested a distal RTA. Because of limitations in urine pH assessment mentioned, further evaluation for distal RTA included an assessment of urine NH₄⁺ excretion. If not initially obvious (non-acidic urine), distal RTA may be unmasked by acid loading (e.g. NH₄Cl). The normal kidney response to acidosis or acid loading is lowering of urine pH and
Increased NH₄⁺ excretion. As most laboratories do not measure urine NH₄⁺, the UAG is used as a qualitative surrogate to estimate NH₄⁺ excretion (Table 1). NH₄⁺ balances the equation for electroneutrality on the Cl⁻ side as the unmeasured cation. Therefore, the UAG becomes more negative as NH₄⁺ excretion increases, assuming minimal HCO₃⁻ in the urine (exclude proximal RTA first). A negative UAG (>−20 mmol/L) is indirect proof of appropriate increased NH₄⁺ excretion, suggesting a nonrenal cause for the normal anion-gap metabolic acidosis. When very little NH₄⁺ is produced, the UAG remains positive, suggesting a renal cause.

There are limitations of the UAG. It assumes that Cl⁻ is the major anion accompanying NH₄⁺. This may not be true if large quantities of other anions are present, such as ketones and anionic drugs such as penicillins. In this case, it is useful to estimate urine NH₄⁺ by calculating the UOG, which is the difference between measured and calculated urine osmolality (Table 1). This test detects NH₄⁺ regardless of the anion excreted with it. The urine NH₄⁺ is approximately half the UOG. A NH₄⁺ excretion >75 mmol/L is an appropriate renal response to prevailing acidosis while a NH₄⁺ excretion <25 mmol/L is an inappropriate response. In our patient, the urine NH₄⁺ estimated from the UOG was consistent with the UAG, indicating that ceftriaxone (a renal-excreted anionic drug) did not significantly interfere with UAG estimates of urine NH₄⁺. The persistently positive UAG and urine NH₄⁺ <15 mmol/L confirms distal RTA.

As gastrointestinal loss or RTA may lead to metabolic acidosis and dyskalaemia, examining renal tubular K⁺ handling may be informative. The TTKG is a useful surrogate for distal tubular K⁺ secretion (Table 1) and may be used to assess the appropriateness of renal K⁺ excretion during dyskalaemia. The TTKG estimates the tubular K⁺ concentration in the cortical collecting duct, where tubular fluid is isotonic to plasma. The formula uses the urine-to-blood osmolality ratio to correct for water reabsorption, which subsequently occurs in the medullary collecting duct and leads to a higher K⁺ concentration in the collected urine. An appropriate TTKG is typically <4 with hypokalaemia and >6 with hyperkalaemia. Hypokalaemia and TTKG >4 suggests renal potassium wasting (type 1 or 2 RTA). Hyperkalaemia and TTKG <6 suggests type 4 RTA (inability to excrete K⁺ and low aldosterone response). Our patient had TTKGs ≥10 with hypokalaemia, consistent with type 1 RTA.

The TTKG has limitations. The urine Na⁺ should be >25 mmol/L to exclude low Na⁺ delivery as the rate limiting factor in K⁺ secretion. The urine osmolality should be greater than plasma osmolality, as vasopressin is required for maximal secretion of K⁺. The formula also assumes no significant reabsorption of osmoles in the medullary collecting duct, a view recently questioned. Because of some urea reabsorption and recycling, it is likely that the formula overestimates the concentration of K⁺ in the cortical collecting duct. Thus, mild abnormalities in the TTKG may be explained by variations in urine excretion and should be interpreted with caution.

A more practical alternative to the TTKG is the urine K⁺ to creatinine ratio (U K/UCr). As creatinine excretion is nearly constant, this ratio corrects for variations in urine volume. The expected U K/UCr in hypokalaemia and hyperkalaemia is <1.5 and >20 mmol K⁺/mmol creatinine respectively. In our patient, the U K/UCr was inappropriately high at 8.2 ± 2.9 mmol K⁺/mmol creatinine (n = 11) on admission and follow up, consistent with the TTKG findings of renal K⁺ wasting. Furthermore, gastrointestinal K⁺ loss is usually associated with renal Na⁺ conservation (U osm < 20 mmol/L or FENa < 1%), while RTA demonstrate high U osm (FENa > 2–3%). Our patient’s U osm was 64 ± 16 mmol/L (range, 40–95 mmol/L), with a FENa of 3.2 ± 0.8% (range, 1.8–3.7%).

Relevant to our case, type 1 RTA is associated with autoimmune disease, drugs and thyroid disorders. Both primary and secondary Sjogren syndrome is associated with type 1 RTA. Absence of H⁺-ATPase and autoantibodies to intercalated cells in the distal nephron has been described, suggesting a defect in distal H⁺ secretion. Similarly, proton pump inhibitors, which block H⁺-K⁺-ATPase, have been reported to exacerbate type 1 RTA. Interstitial inflammation is often found in renal biopsies but other than case reports, there is no consensus on steroid treatment for RTA. Type 1 RTA is less commonly reported with systemic lupus erythematosus, primary biliary cirrhosis, autoimmune hepatitis and autoimmune thyroiditis. Rarely, it is said to occur with fibrosing alveolitis, polyarteritis

<table>
<thead>
<tr>
<th>Description</th>
<th>Symbol</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine anion gap</td>
<td>UAG</td>
<td>((\text{U}<em>{\text{Na}} + \text{U}</em>{\text{cl}}) - \text{U}_{\text{cr}})</td>
</tr>
<tr>
<td>Urine osmol gap</td>
<td>UOG</td>
<td>(\text{U}<em>{\text{osm}} - [2 \times (\text{U}</em>{\text{Na}} + \text{U}<em>{\text{K}}) + \text{U}</em>{\text{urea}} + \text{U}<em>{\text{glucose}}] \times 0.5 \times \text{U}</em>{\text{Osm}})</td>
</tr>
<tr>
<td>Urine ammonium</td>
<td>(U_{\text{NH}_4})</td>
<td>(0.5 \times \text{U}_{\text{Osm}})</td>
</tr>
<tr>
<td>Transtubular potassium gradient</td>
<td>TTKG</td>
<td>(\frac{\text{U}<em>{\text{cr}}}{\text{U}</em>{\text{cr}} + \text{U}_{\text{osm}} / \text{Blood osm}} \times \text{Blood K}^+)</td>
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<tr>
<td>Urine K⁺/Urine creatinine ratio</td>
<td>(U_{\text{K}}/U_{\text{cr}})</td>
<td>(\frac{\text{U}<em>{\text{K}}}{\text{U}</em>{\text{cr}} + \text{U}_{\text{cr}}})</td>
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<td>Fractional excretion of bicarbonate</td>
<td>FE bicarbonate</td>
<td>(\frac{\text{U}<em>{\text{bic}}}{\text{U}</em>{\text{cr}}} \times \text{Blood HCO}_3^- / \text{Blood cr} \times 100)</td>
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<td>Fractional excretion of sodium</td>
<td>FE sodium</td>
<td>(\frac{\text{U}<em>{\text{Na}}}{\text{U}</em>{\text{cr}}} \times \text{Blood Na}^+ / \text{Blood cr} \times 100)</td>
</tr>
</tbody>
</table>

**cr**, creatinine; **osm**, osmolality; **U**, urine.

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nodosa and cryoglobulinaemia. It may occur with hypergammaglobulinaemia, from haematological disease or human immunodeficiency virus.

RTA due to medications is usually type 2 or 4. Type 1 is associated with amphotericin B, ifosfamide, lithium, foscarnet and analgesics. Non-steroidal anti-inflammatory drugs typically cause type 4 RTA but two recent reports described distal RTA and hypokalaemia associated with ibuprofen-codeine. The authors suggest that carbonic anhydrase inhibition may be responsible for COX-2 inhibitors like celecoxib. Our follow-up data suggest that celecoxib may have exacerbated underlying RTA rather than being causative.

Hypothyroidism is associated with incomplete distal RTA and experimental defects in distal renal acidification. Both type 1 and 4 RTA has been reported with non-autoimmune hypothyroidism. Type 1 RTA is also reported with autoimmune hypothyroidism. Furthermore, there is a high prevalence of concurrent thyroid autoantibodies in patients with Sjögren syndrome. In some cases, thyroid hormone replacement improves RTA so it is unclear if autoimmunity is required for RTA to manifest. Our patient did not have thyroid antibody testing but was euthyroid.

Diagnosis of RTA can be achieved by serial analysis of blood and urine without an acid-loading test. The contribution of drugs to RTA should be considered, and patients should be evaluated for systemic disease, including autoimmune and thyroid disorders.

Acknowledgements

We thank Dr Andrew Campbell (Dandenong Hospital, Melbourne, Victoria) for his assistance in organising the follow-up tests for our patient.

References


General health of opioid substitution therapy clients
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Key words
opioid substitution therapy, hepatitis C, cardiovascular disease, obesity, drug user.

Abstract
Five common medical conditions among opioid substitution therapy (OST) clients were assessed during a health promotion event held at a tertiary hospital-based OST clinic in Sydney, Australia. Data were collected anthropometrically (body mass index and waist circumference), using spirometry, electrocardiogram, Pap test histories, Fibroscan and medical record review. Assessments were undertaken by specialised hospital staff. Abnormal results were found for 17% of those who underwent an electrocardiogram, 60% were anti-hepatitis C virus positive (40% were viraemic), fibrosis was detected in one-third (7% severe fibrosis and 18% cirrhosis), chronic obstructive pulmonary disease was detected among 30% of participants with 7% at Global Initiative for Chronic Obstructive Lung Disease stage II and 2% at stage III. Forty-seven percent of the female respondents reported that they had not had a Pap test in the previous 2 years. Findings indicate that OST clients suffer several health problems that OST clinics are well placed to identify and provide support for referrals.

Opioid substitution therapy (OST) clients suffer substantial morbidity and mortality, and their overall health is generally poorer than that of the general population.¹ Blood-borne viral infections, particularly hepatitis C virus (HCV) and human immunodeficiency virus, and mental health problems are some of the well-known and highly researched issues in the literature.²⁻⁵ These common health issues often overshadow a range of general health problems, such as diet and obesity, cardiac health issues, including prolonged QT interval related to opioid use, lung function and sexual health. These issues are often exacerbated by poor nutrition and high rates of tobacco and alcohol use, and are likely to impact on the degree to which the overall goals of OST are achieved by individual clients. Drug dependence and poor socioeconomic status often results in healthcare being a low priority for these clients, and indolent or non-urgent health problems may remain unknown until the condition becomes severe.⁴ Moreover, to date, much of what is known about OST clients’ general health is largely based on psychometric survey questionnaires.⁵

This study assessed the prevalence of five common medical conditions among clients of a public tertiary hospital-based OST clinic. Three of these conditions, obesity, cardiovascular and respiratory health, are Australian chronic disease priority areas,⁶ and liver and sexual health are health priority action areas for this client group. Data were collected during a health promotion event as part of International Hepatitis Day held at an OST clinic located in a large inner-city tertiary hospital in Sydney. The event provided clients with an opportunity to learn about hepatitis and undergo health assessments being offered onsite at the OST clinic by other hospital departments – gastroenterology and hepatology, cardiology, respiratory, dietetics and sexual health. Pap test histories were collected verbally from female participants during face-to-face interviews. Free dental advice was provided by the Dental Health Department and overdose and cardiopulmonary resuscitation advice provided by the NSW Ambulance Service.

HCV test results (antibody performed by HCV recombinant immunoblot assay and confirmed by enzyme immunoassay and qualitative RNA performed by polymerase chain reaction) available from the participants’ medical files were recorded. Fibroscan, an ultrasound-based instrument that measures transient elasticity and stiffness of the liver expressed in kilopascals (kPa), was used to determine stages of fibrosis indicated by a range
of 2.4–75.4 kPa with values increasing with fibrosis stage. The range 2.4–7.0 kPa (F0-1) indicates no or minimum fibrosis; 7.1–9.4 kPa (F2) indicates portal fibrosis and few septa; 9.5–12.4 kPa (F3) indicates numerous septa without cirrhosis; and >12.5 kPa indicates probable liver cirrhosis. Potential cardiac and pulmonary function abnormalities were screened using electrocardiogram (ECG) and spirometry. Body mass index (BMI; kg/m²) and waist circumference were calculated anthropometrically.

Patients were seen within a marquee directly outside the OST clinic. Examination couches were provided and screens allowed privacy. Data were analysed using STATA (StataCorp. Stata Statistical Software, Release 11; College Station, TX, USA). Approval was obtained from the Royal Prince Alfred Hospital Ethics Committee.

On the day of the health event, OST was dispensed to 133 clients and 17 clients had a medical or counselling appointment. Fifty-eight (39%) clients participated in the event. Participants’ mean age was 41 (range 21–66) years (cf. clinic population mean age 40.2 years, range 21–66). Nineteen percent of participants were Aboriginal or Torres Strait Islanders (cf. 25% of clinic cohort), and 57% were female (cf. 50% clinic cohort; Table 1). Thus, our sample is largely representative of the clinic client cohort.

The mean BMI was 26.4: >25 for almost half (47%) and >30 for a quarter of the participants. However, waist circumference exceeded the healthy threshold (94 cm for males and 80 cm for females) for 48% of men and 68% of women.

Abnormal ECG results were found in 17% of the participants who underwent testing (Table 2). Two female participants on 110 mg and 125 mg methadone were identified with prolonged QT. The QT/QTc interval of the former was 518/477 ms; information was unable to be retrieved for the latter. Necessary arrangements were made for further monitoring of these participants.

Almost all (93%) participants were current smokers. Spirometry revealed the ratio of forced expiratory volume in 1 s and the forced vital capacity (FEV1/FVC) was <0.70 for almost one-third of the participants with 7% at stage II and 2% at stage III of chronic obstructive pulmonary disease (COPD) based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric criteria. Of the 21 female participants who provided information about recent Pap screening, 48% reported no testing in the previous 2 years.

According to medical records, 30 participants (60%) were anti-HCV positive and 22 (40%) were HCV RNA positive. Forty-four participants underwent liver stiffness assessment using FibroScan (Echosens, Paris, France); the mean score was 11.19 (range 2.2–72). Some degree

<table>
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<th>n (%)</th>
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<tr>
<td>≤45 years</td>
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<tr>
<td>&gt;45 years</td>
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<tr>
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<tr>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Methadone</td>
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<td>BMI &gt;25 (overweight/obese)</td>
<td>25 (47)</td>
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<tr>
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<td>8 (19)</td>
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<td>4 (9)</td>
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<tr>
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<td>2.4–7.0 kPa (F0-1)</td>
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<td>7.1–9.4 kPa (F2)</td>
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</tr>
<tr>
<td>9.5–12.4 kPa (F3)</td>
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<td>&gt;12.5 kPa (F4)</td>
<td>8 (18)</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, global initiative for obstructive lung disease; HCV, hepatitis C virus; OST, opioid substitution therapy; PCR, polymerase chain reaction.
of fibrosis was indicated in one-third of participants; severe fibrosis was indicated for 7% and cirrhosis for 18%.

Arrangements were made for referrals within the same tertiary hospital following the health event where further assessment or follow up was required (47%). Forty percent of those referrals were ascertained as attended.

The findings show that, in addition to the commonly acknowledged health issues of hepatitis and liver disease, OST clients experience a range of health problems. Despite the limitations of the small sample size and narrow range of diagnosis, this study suggests that OST clients have a higher prevalence of COPD stage II–IV (11.6% cf. 5%) and of stage I (19% cf. 3.7%), and lower rate of Pap test than the general population (43%).

QTc prolongation was identified in two participants. QTc prolongation, albeit a rare complication associated with methadone, may predispose susceptible patients to ventricular arrhythmias specifically torsade de pointes. QTc prolongation is thought to be dose related where doses exceed 150 mg, but neither of the two participants (cf. 110 and 125 mg) in this study received such doses. Indeed, our results support the recommendation against blanket screening of methadone patients unless indicated by dose, family or medical history. Nonetheless, necessary arrangements of referrals and further diagnosis were made for these participants.

Overall, a lower proportion of participants had a BMI >25 than the general adult population of Australia (47% vs 61%). When considering obesity alone, the prevalence in our sample (24%) is similar to the 2007–2008 national prevalence of 21%. Waist circumference, however, which is increasingly being preferred as a measure of risk factors for diabetes, was above the threshold for more than half of the participants, albeit similar to the Australian population. Weight gain is common in methadone-maintained patients, and preclinical trials have found that chronic exposure to mu-opiate agonism is associated with weight gain. However, the relationship between BMI and OST in this sample is unclear because clients’ weight prior to commencing OST is unknown.

One of the key findings of the study was poor respiratory health. Tobacco smoking has been well documented among this population, and the vast majority of participants in this study were smokers. Previous work on smoking cessation with this population, however, has shown a low success rate despite reported interest in cessation programmes. More than one-third of our sample met criteria for COPD, and this emphasises the need for continued efforts in this area and suggests even modest results about smoking cessation may have a substantial benefit.

Although already well established, the high prevalence of HCV-related liver disease among OST clients, particularly those with a history of illicit drug injection, is a serious global health concern. Despite the increasing safety and efficacy of HCV treatment, uptake among OST clients remains low. Our results, which indicate that almost one-in-five participants are likely cirrhotic, highlight the urgency for appropriate HCV treatment delivery models targeting this population.

A slightly higher proportion of female participants (48%) reported no Pap test in the previous 2 years than females nationally (43%), and that reported by the female participants of Illicit Drug Reporting System (41%). This is nonetheless disturbing given recent work showing women aged 20–54 years with a drug-related admission to NSW hospitals are at increased risk of cervical abnormalities, cervical cancer and reported less screening than women with no drug-related hospital admission. The findings emphasise the need for targeted gynaecological services for this group, including integrated care models.

Although scant research has documented referral uptake among OST clients, only 40% uptake of referrals made within the same tertiary hospital is notable. The often complex nature of OST clients’ social circumstances and the opportunistic nature of the screening process may have impeded clients’ referral attendance. Enhanced referral, as has been successfully used in outreach setting with people who inject drugs, may be a more appropriate model referral with this population.

In addition to the low response rate (43%), the key limitation of the study was use of some selective diagnostic tests based on their convenience in screening and practical delivery in the study context rather than their diagnostic sensitivity. Spirometry, for example, is dependent upon patient cooperation and effort, and thus COPD prevalence can be underestimated.

Despite these limitations, this study presents clinical results on important medical conditions experienced by a vulnerable group. It is important that OST clients are offered appropriate healthcare. Although it may be unfeasible to routinely offer the extent of diagnostic screening described herein, many public OST clients in NSW are located within large tertiary hospitals and thus a broader approach to clients’ health should be feasible. The provision of onsite primary healthcare, which utilises clients’ regular attendance for dosing, may enhance referral uptake and facilitate linkage to other healthcare facilities. The available evidence suggests such an approach can be effective, and such efforts may improve the health and quality of life of clients and OST retention.
Acknowledgements

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Two rare cases of Epstein–Barr virus-associated lymphoproliferative disorders in inflammatory bowel disease patients on thiopurines and other immunosuppressive medications

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Key words
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Abstract
The setting of chronic immunosuppression in inflammatory bowel disease (IBD) may promote the proliferation of Epstein–Barr virus-positive neoplastic clones. We report two rare cases of Epstein–Barr virus-associated lymphoproliferative disorder in IBD patients: one resembled lymphomatoid granulomatosis, and the other was a lymphoma resembling Hodgkin lymphoma. There are currently no guidelines for the prevention of lymphoproliferative disorder in IBD patients on immunosuppressive therapy.

Lymphoma in immunosuppression exhibits common biologic features, including derivation from the B-cell lineage, extranodal involvement, rapid clinical progression and an association with Epstein–Barr virus (EBV) infection. Lymphoma cases complicating inflammatory bowel disease (IBD) are typically B-cell post-transplant lymphoproliferative disorders (LD), which is usually EBV positive.1 We report two rare cases of EBV-associated LD in IBD patients: one resembled lymphomatoid granulomatosis, and the other was a primary extranodal Hodgkin lymphoma.

A 42-year-old woman with gastroduodenal, jejunal and ileocolonic Crohn disease (CD) presented with a 3-month history of dyspepsia, fever, night sweats, weight loss and worsening respiratory symptoms. She had been on corticosteroids and sulphasalazine after the initial diagnosis of CD at age 18, then 6-mercaptopurine (6-MP) 75 mg (1.2 mg/kg) with good response for the last 5.5 years. Her extraintestinal manifestations included inflammatory arthritis. She was a non-smoker and was otherwise well except for childhood asthma and eczema. Her family history included two cousins with CD, sister had hyperthyroidism and a paternal grandmother had colorectal cancer.

A diagnosis of EBV-associated LD with features similar to lymphomatoid granulomatosis was made on histopathology obtained from a large necrotic gastric ulcer and a necrotic pulmonary nodule (Fig. 1) with confirmed EBV-encoded RNA in situ hybridisation (EBER-ish) positive cells (Fig. 2). Serum EBV viral load (EBV-VL) was $1.4 \times 10^5$ copies/mL on presentation. A staging positron emission tomography–computed tomography (CT) scan confirmed extranodal disease above and below the diaphragm, including extralymphoid sites such as left temporal lobe, left thyroid lobe and lower lobes of both lungs. CT brain scan revealed a ring-enhancing lesion in left temporal lobe; a stereotactic biopsy was considered high risk, and magnetic resonance (MR) spectroscopy was not diagnostic. Empirical treatment for toxoplasmosis was commenced considering lymphopenia and low CD4 count.

Considering overlap features between lymphomatoid granulomatosis and EBV-associated LD, she initially
Interferon 7.5 mIU thrice weekly and 10 days later was changed to rituximab 375 mg/m² etoposide 50 mg/m² prednisone 60 mg/m² vincristine 0.4 mg/m² cyclophosphamide 750 mg/m² doxorubicin 10 mg/m² immunochemotherapy with granulocyte colony-stimulating factor 5 μg/kg from day 6 to recovery of neutrophils. Following two cycles of treatment, she developed expressive dysphasia and cranial nerve palsy. An MR brain scan revealed multiple lesions in right cerebellum, pons, occiput, left frontal lobe and left corpus callosum, so she underwent whole-brain radiotherapy and commenced one cycle of Arm B rituximab and fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, with infusional cytosine arabinoside 3000 mg/m² q12h days 2 and 3 and infusional methotrexate 1000 mg/m² d1 with folinic acid rescue.

Figure 1 Lung nodule with necrosis; necrotic vessel seen in the centre (haematoxylin–eosin).

Figure 2 Numerous mononuclear cells with Epstein–Barr virus (EBV)-positive nuclei on EBV-encoded RNA in situ hybridisation.

Her progress was complicated by extensive deep vein thrombosis, multiple falls, malnutrition and sepsis. Approximately 5 months after diagnosis, she died from resistant disease involving the central nervous system.

A 30-year-old man with ongoing problems with severe perianal CD presented with severe left iliac fossa pain due to a colonic perforation and underwent a total colectomy and end ileostomy. Histological analysis demonstrated a primary extranodal EBV-positive Hodgkin lymphoma affecting the descending colon. There was no evidence of disease affecting the resection margins or draining lymph nodes.

He was diagnosed with CD 6 years prior to his presentation and was treated initially with 6-MP 100 mg (1.5 mg/kg) daily and intermittent courses of corticosteroids. Approximately 4 years after diagnosis, he relapsed after stopping maintenance 6-MP therapy; colonoscopy revealed severe Crohn colitis with superficial and deep ulcers, and a tight anorectal stenosis. Prior to his presentation, he had been on multiple medications, including certolizumab pegol for approximately 9 months (stopped 12 months prior to his presentation), sirolimus for 3 months (stopped 12 months prior to his presentation), intermittent courses of prednisone and infliximab for four doses (ongoing at time of presentation) and multiple courses of antibiotics, including metronidazole and ciprofloxacin. He continued 6-MP over the entire period.

He had ongoing problems with progressive anorectal disease for approximately 12 months, culminating in a defunctioning loop ileostomy 3 months prior to his presentation with perforation. During that period, MR imaging of the perineum revealed thickening of the anorectal region, with a perianal sinus tract at the level of the external anal sphincter. Subsequent flexible sigmoidoscopy and examination under anaesthesia (EUA) showed ulceration of the perineum, active inflammation of the rectosigmoid mucosa with serpiginous ulcers extending to 45 cm, an anorectal stenure that was dilated and a presacral abscess that was curetted. A second EUA later showed erythematous and friable rectosigmoid mucosa to 20 cm and severe fissuring ulcers of the anal canal, but no evidence of abscess formation. A decision was made to proceed to a defunctioning procedure because of refractory anorectal disease.

He underwent completion proctectomy 7 months after presentation with perforation. This showed active CD but no evidence of lymphoma in the anorectum or associated nodes. He has completed doxorubicin 25 mg/m² days 1 and 15, bleomycin 10 000 IU/m² days 1 and 15, vinblastine 6 mg/m² days 1 and 15, dacarbazine 375 mg/m² days 1 and 15, and chemotherapy, and is currently in remission.

The risk of developing an LD is increased in patients taking thiopurines. A recent Dutch nationwide study
demonstrated a correlation between immunomodulator use in IBD and EBV-positive lymphoma. Almost all patients with an EBV-positive lymphoma used a thiopurine, and these EBV post-transplantation-like lymphomas were particularly prevalent in those aged <50 years. The CESAME study of a French cohort of 19 486 IBD patients also showed an increased risk in those taking thiopurines and calculated that the overall multivariate hazard ratio for developing an LD from thiopurine use was 5.28 (95% confidence interval 2.01–13.9). Although the absolute risk of developing lymphoma is low, it increases with age: 1 in 4357 for ages 20–29 years and 1 in 355 for ages 70–79 years. Most cases of LD in IBD patients on thiopurines are post-transplantation LD (PTLD) of B-cell origin and are EBV-positive (60–70%). The risk of primary intestinal LD is also highest in those exposed to thiopurines; these tumours are also commonly EBV-positive (45.5% of cases).

There are four categories of PTLD: early lesions, polymorphic PTLD, monomorphic PTLD and classical Hodgkin lymphoma. Classical Hodgkin lymphoma-type PTLD is a rare form: the histological features are similar to that of Hodgkin lymphoma in immunocompetent subjects, and almost all are EBV positive. In addition to our case, we are aware of only 15 other cases of primary gastrointestinal Hodgkin lymphoma complicating CD. All seven cases tested for EBV were positive.

Lymphomatoid granulomatosis in CD is also very rare and is associated with thiopurine therapy and EBV virus infection. It has been described in a teenage patient with CD. The new World Health Organization classification recognises several entities characterised by EBV infection of the tumour cells, including lymphomatoid granulomatosis, EBV-positive diffuse large B-cell lymphoma of the elderly and EBV-positive mucocutaneous ulcer with Hodgkin-like features, which is a newly recognised clinicopathological entity and has a self-limited, indolent course. It is associated with advanced age and immunosuppression.

Approximately 80% of LD in organ transplant patients on immunosuppression are positive for EBV, and EBV-VL appears to be a good predictor of their development. EBV-VL does not appear to differ significantly between CD patients and EBV-seropositive controls, nor is it influenced by disease activity or immunosuppressive therapy, including infliximab. However, some patients with CD do have transient, very high viral loads that are compatible with an increased risk of PTLD. In spite of this and because the absolute risks are very low in IBD patients, monitoring EBV status is not recommended by any expert authority. Nevertheless, there may be a role for monitoring EBV-VL to guide therapy in certain situations, such as treatment with infliximab for those who have a previous history of lymphoma and positive EBV serology. An alternative approach in such patients is to use medications such as methotrexate, which may not be associated with such a large increase in the risk of developing LD as the thiopurines. The risk for those on single-agent anti-tumour necrosis factor therapy also appears to be less than for those on thiopurines alone, and it may be prudent to cease thiopurine usage in those patients who are stable after induction of remission using combination therapy.

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Mycobacterium mimicking metastatic melanoma

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Key words
Mycobacterium, malignancy, melanoma, mimic.

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Abstract
We present three patients with lung nodules with an antecedent history of primary cutaneous melanoma or metastasis of melanoma to extrathoracic lymph nodes. Based on radiological findings, it was suspected that these patients had metastatic disease. Subsequent investigations confirmed the cause of the nodules was non-tuberculous mycobacterial infection. We discuss the similarities in symptoms and radiological features between atypical mycobacterial infections and metastatic disease and why a biopsy is important prior to planning a patient’s treatment.

Diagnosing lesions based on radiological pathognomonic features has its hazards. In a case series of 100 patients who had a stereotactic biopsy of a brain lesion, 19% had different clinical and radiological diagnoses preoperatively and postoperatively.1 In a retrospective study of 229 patients with an antecedent history of melanoma who had undergone a biopsy of a suspicious lung nodule, malignancy was confirmed in 88% of patients.2 The diagnosis of metastatic melanoma was made in only 69%; 14% had a new primary lung cancer, and 5% had a non-melanoma metastasis. This highlights the importance of tissue diagnosis before decision-making regarding treatment. In addition, the emergence of molecularly targeted therapy has placed further importance on biopsying suspected secondaries, as metastatic lesions may harbour different receptor mutations from the primary cancer. In a prospective study of 121 breast cancer patients, biopsy of a metastatic lesion led to a change in management for 17% of women.3 This case report highlights the importance of considering a biopsy prior to embarking on a management plan based on radiological findings alone.

In July 2008, JB (case 1), a 55-year-old man, had an excision of an ulcerated scalp melanoma with Clark’s level 4 invasion, 4.2 mm Breslow thickness. A staging positron emission tomography (PET) scan showed a right middle lobe fluorodeoxyglucose (FDG)-avid mass and no other suspicious lesions (Fig. 1). A computed tomography (CT)-guided fine-needle aspirate of this mass was abundantly cellular and contained cells with ovoid nuclei exhibiting moderate enlargement and variation. Some cells contained pigment in keeping with melanin, and it was concluded that this right lung mass was metastatic melanoma. In August 2008, JB underwent a right middle lobectomy with minimal postoperative complications.
The histopathology was reported as necrotising and suppurative granulomatous inflammation, with no evidence of primary or metastatic malignancy. *Mycobacterium kansasii* was cultured from the specimen. JB has had two more years of clinical follow up with regular PET scans and has been disease-free.

JH (case 2), a 34-year-old woman, presented in September 2010 with a painful mass in her left axilla. This initially responded to antibiotics, but she re-presented a month later with recurrence of mass. An ultrasound-guided biopsy confirmed metastatic melanoma. The primary melanoma was never found. She underwent a left axillary dissection in November 2010. This found one out of five lymph nodes positive for metastatic melanoma. JH partly completed adjuvant interferon therapy and also had adjuvant radiotherapy to her left axilla (60 grays, 30 fractions). As part of her surveillance, a CT scan in February 2012 showed multiple pulmonary nodules (measuring up to 9 mm) in the posterior segment of the right upper lobe that were suspicious for melanoma metastases. There were associated tree-in-bud opacities, possibly representing endobronchial spread of tumour. A PET scan was performed, which showed two small metabolically active lung nodules in the right upper lobe, suggestive of metastatic melanoma. No evidence for nodal or solid-organ metastatic disease was seen elsewhere. JH denied any symptoms related to these findings. It was recommended that JH undergo a right upper lobe wedge resection. This was performed in March 2012 with minimal complications. The histopathology reported no malignant cells seen, but necrotising and suppurative granulomatous inflammation was present, and *Mycobacterium intracellulare* was cultured from the specimen.

PB (case 3), an 82-year-old man, had a scalp lesion excised in September 2010. The pathology revealed a nodular melanoma with Clark level 4 invasion, 3.85 mm Breslow thickness. A baseline PET scan in October 2010 revealed moderately metabolically active nodules in the right lung, which appeared inflammatory. In addition, intense bilateral hilar, subcarinal and anterior mediastinal nodal uptake suggested an inflammatory process, but infiltration could not be excluded, and follow up with a repeat PET scan in 3 months was suggested and carried out in January 2011. It was noted that FDG uptake in the small mediastinal nodes was more intense on this scan than in the previous one. There was also progressive uptake related to previous and new pulmonary nodules, particularly on the right. The overall appearance and progression were suggestive of metastatic melanoma.

*Figure 1* Case 1: Positron emission tomography scan of the right middle lobe lesion prior to surgery.
disease. An endobronchial ultrasound transbronchial needle aspiration (EBUS TBNA) was arranged. This showed no evidence of metastatic malignancy, lymphoproliferative disorder or granulomatous inflammation. PB was placed back on surveillance, with a repeat PET scan in April 2011 and CT scans in August 2011 and December 2011 showing stable disease. In March 2012, a repeat PET scan confirmed new metabolically active lung nodules in the right and left lungs and persistent metabolic activity in the mediastinal and hilar lymph nodes (Fig. 2). On further review, it was noted that Mycobacterium abscessus had been cultured from the EBUS TBNA back in April 2011. Despite radiological progression, the patient remained asymptomatic, and it was decided that PB should be placed on a period of observation before commencing antibiotics. In August 2012, PB developed a new lesion on his right fourth rib; this was biopsically proven to be metastatic B-RAF mutation-positive melanoma. PB was diagnosed with recurrent, metastatic melanoma in his right fourth rib as well as an atypical mycobacterial infection, as the lesions in his lung and mediastinal lymph nodes remained stable in appearance despite progression of disease elsewhere.

It is often difficult to differentiate malignancy from mycobacterial infections guided by radiological features alone. There are numerous cases in the literature where mycobacterial infections mimic malignancy, including patients presenting with solitary lung nodules, breast lesions, bone lesions and disseminated disease. In recent years it has come to light that a prominent

Figure 2 Case 3: Positron emission tomography scan of right lung nodules and multiple bilateral mediastinal and hilar lymph nodes. Left, January 2011. Right, April 2011.
Austalian championing diet and intensive meditation as a cure for metastatic osteogenic sarcoma may have had disseminated tuberculosis rather than metastatic disease, having survived 37 years after the diagnosis of secondaries from sarcoma. We report three cases where, based on the clinical picture and radiological findings, atypical non-tuberculous mycobacterial infections were mistaken for metastatic melanoma.

Non-tuberculous mycobacteria (NTM) are free-living organisms that are ubiquitous in the environment. They have been cultured from surface water, tap water, soil, domestic and wild animals, milk and food products. These organisms can also inhabit body surfaces or secretions without causing disease. The common pathogens involved are the *Mycobacterium avium* complex (*M. avium, M. intracellulare*), *M. kansasi*, *M. ulcersans* and the rapidly growing mycobacteria (*M. fortuitum, M. chelonae* and *M. abscessus*). The symptoms of non-tuberculous lung disease are non-specific. They include cough (productive or dry), fatigue, malaise, weakness, dyspnoea, chest discomfort and occasionally haemoptysis. These symptoms may also be present in patients with lung metastases, thus making non-tuberculous lung disease difficult to diagnose clinically.

Radiologic signs of NTM infections include nodular or reticulonodular infiltrates, cavities, multifocal bronchiectasis and/or multiple small nodules. Metastatic disease can often simulate these signs, as there are no pathognomonic radiographic features that distinguish metastatic disease from other, benign processes. In patients with a previous history of cancer, metastatic disease is a strongly considered differential. In a series of 1104 patients who had undergone resection of a solitary pulmonary nodule, 79% of patients with a history of extrapulmonary cancer had undergone resection of a solitary pulmonary nodule, 79% of patients with a history of extrapulmonary cancer had a malignant lesion excised (non-small-cell lung carcinoma 41%, metastases 38%). PET scans may also be used to elucidate the aetiology of lung nodules; however, NTM infections often cause FDG uptake. In a review of 16 studies and 220 patients with mycobacteriosis, 90% of patients had PET-avid lesions. Often, serial scans are used to differentiate malignant from benign lesions, as the two types of lesion progress at varying rates. Untreated infections and metastatic disease are expected to progress in time, albeit at different rates, with malignant lesions thought to grow at a faster pace. However, with melanoma, growth is unpredictable, ranging from indolent growth through many years to aggressive growth through a few short weeks. Thus, although the likelihood of metastatic disease is high in a patient with a history of cancer and radiographic findings suggestive of metastases, it is still not possible to reliably distinguish metastases from other differentials based on symptoms and radiographic investigations.

Treatments for metastatic disease and NTM infections significantly differ. Although there are no randomised control trials addressing the management of NTM, it is recommended that treatment involves three to four antibiotics, including a macrolide, for at least 1 year. The treatment for lung oligometastases is resection, as this may offer a long disease-free interval. In those who are not fit enough for resection, palliative chemotherapy may be one of the options offered. However, administering chemotherapy to a patient with an active infection could be deleterious owing to its myelosuppressive side-effects. Taking into account the varying and intensive treatment required, it is imperative that a firm diagnosis of metastasis be confirmed before commencement.

Fine-needle aspiration (FNA) may be inadequate in diagnosing malignancy – as in our first case, where a FNA was performed and results reported as consistent with metastatic melanoma. A meta-analysis showed that the false-positive rate of a transthoracic FNA is low (0.09). Even with FNA’s low false-positive rate, in a patient with atypical radiological findings and disease course, continued clinical suspicions should be upheld, and repeat biopsies may be required.

New lesions that develop in patients with a history of antecedent cancer should be considered for biopsy to obtain histological confirmation of presumed metastatic disease before embarking on treatment. The clinical picture might be highly suggestive of metastatic disease, but as illustrated by these cases, NTM infections might mimic metastatic disease. In addition to the need to differentiate benign conditions that mimic cancer, the presence of a different primary cancer needs to be excluded, as patients who have had one cancer are often at increased risk of a second. Last, in an era of targeted treatments, molecular tests for mutations are often needed to guide treatments, and thus biopsies of presumed metastatic lesions can help guide subsequent treatment.

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**PERSONAL VIEWPOINT**

**Product information for generic drugs: old, unloved and sometimes unsafe**

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**Key words**

pharmaceutical preparation, product information, drug therapy, medication error, drug labelling, prescribing.

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**Abstract**

Product information is often at odds with current evidence and guidelines and inconsistent between products and within classes. There is no single ‘owner’ responsible for up-to-date medicines product information. Outdated product information increases the risk of inappropriate prescribing.

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The approved Product Information (PI) for many medicines is outdated with no single ‘owner’ responsible for up-to-date information on safety and efficacy. Outdated safety information can result in harm if decisions are
Table 1 Examples of ‘errors’ in drug information that emerge over time with inconsistencies between product information and evidence-based care

<table>
<thead>
<tr>
<th>Out of date information</th>
<th>Example</th>
<th>Potential consequence</th>
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<tbody>
<tr>
<td>Wrong doses</td>
<td>Colchicine</td>
<td>Over or under dosing</td>
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<tr>
<td>Wrong dose intervals or monitoring targets</td>
<td>Gentamicin</td>
<td>Over or under dosing</td>
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<tr>
<td>Inappropriate contraindications</td>
<td>Metformin – GFR &lt;60 mL/min</td>
<td>Failure to treat</td>
</tr>
<tr>
<td>Missing indications</td>
<td>Amitriptyline – neuropathic pain</td>
<td>Failure to treat</td>
</tr>
<tr>
<td>Between brand inconsistencies</td>
<td>Venlafaxine</td>
<td>Inconsistencies in treatment and confusion for prescribers and patients</td>
</tr>
<tr>
<td>Within class inconsistencies</td>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Inconsistencies in treatment and confusion for prescribers and patients</td>
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<tr>
<td>Irrelevancies</td>
<td>Drug interactions with terfenadine</td>
<td>‘Alert fatigue’ and irrelevant information obscuring relevant information</td>
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GFR, glomerular filtration rate.

made based on wrong information. Outdated efficacy information can result both in unnecessary treatment and in failure to treat. PI can differ between brands of the same medicine and are usually inconsistent between medicines in the same class. Such inconsistent information contributes to confusion and poor prescribing decisions (Table 1).

All prescription medicines are required to have a PI approved by the Therapeutic Goods Administration (TGA), which can only be amended with TGA approval. During 2005–2007, the TGA held a series of consultations and developed discussion papers around improving consumer and professional access to PI and Consumer Medicine Information (CMI). Subsequently, these resources were provided on the TGA website. An important reason for this was to provide up-to-date information that includes all safety-related updates to PI and CMI. Access to the sponsors’ PI and CMI has been vastly improved by having them on the TGA website, but the information is often neither reliable nor up-to-date.

At present, the sponsor is responsible for keeping a PI up to date. For a new medicine, there is a single manufacturer able to provide accurate and current safety and efficacy information at the time of drug registration. However, once a drug is off patent, there are usually multiple manufacturers of the same medication. PI may vary between brands, and no single manufacturer retains ‘ownership’. Hence, the PI for most medicines are largely frozen in time. For example, the PI for multiple drugs warn of drug interactions with terfenadine, a drug not available in Australia since the late 1990s. There are few incentives to update the PI; rather, there is cost and resource disincentives.

Some independent sources of medicines information, such as The Australian Medicines Handbook, and independent therapeutics information, such as Therapeutic Guidelines, are regularly and systematically updated and have greater consistency between drugs. However, other widely used sources of medicines information, including electronic prescribing software packages, provide their information directly from the PI.

Outdated PI can affect the safe use of medicines. For example, colchicine is effective in the management of acute gout, but it has a narrow therapeutic index and several deaths have been reported. Unintentional toxicity is more common than intentional overdose and is often associated with a poor outcome. In 2007, the TGA required updates to the Colgout and Lengout PI, limiting colchicine use to situations where treatment with non-steroidal anti-inflammatory drugs is contraindicated, failed or not tolerated, and limiting the maximum dose to 6 mg over 4 days in otherwise healthy adults. Since then, a randomised control trial demonstrated that low-dose colchicine (1.8 mg total over 1 h) was non-inferior to high-dose colchicine (4.8 mg total over 6 h) with significantly less toxicity. In 2010, NPS RADAR issued a bulletin recommending low-dose colchicine, and the Australian Medicine Handbook was updated to recommend ‘1 mg as soon as possible, then 500 mcg 1 h later (maximum 1.5 mg per course)’. However, the PI for colchicine have not been updated.

Outdated PI can compromise effective use of medicines. For example, the many PI for metformin include ‘renal failure or renal dysfunction (creatinine clearance <60 mL/min)’ as a contraindication to metformin, whereas some clinical guidelines and evidence-based resources support prescribing the drug to patients with stage 3 chronic kidney disease. For example, the Australian Medicine Handbook recommends using metformin until the creatinine clearance is <30 mL/min. The restriction that remains in the PI may result in patients not being treated with the drug with the best evidence base for treating type 2 diabetes.

Generic medicines, by definition, have the same active substances and have demonstrated bioequivalence. Despite this, PI and CMI can and do vary between brands. Inconsistencies between PI for allopurinol were recently highlighted in a submission by the Australian Rheumatology Association to the Transparency Review Secretariat of the TGA. Some PI and CMI for allopurinol suggest dosing allopurinol based on the severity of the gout, while others recommend dosing allopurinol to target
uric acid concentration. Different azathioprine PI have different recommendations on dosing related to food. Different venlafaxine PI have different indications. Such discrepancies between PI imply differences between brands that do not exist.

If PI are to be provided, a single up-to-date PI is required for each generic medicine – this is not currently the case. With multiple manufacturers of generic medicines, this is unlikely to be achieved within the current system. Mandating that generic drug manufacturers update their PI as new data become available is unlikely to be the solution. First, this would result in more differences between PI rather less. Second, generic medicine manufacturers are unlikely to have the resources or the required expertise in post-marketing pharmacovigilance.

We suggest that a single body, such as the TGA, should be responsible for maintaining the PI and the consumer information for all generic prescription medicines in Australia. The TGA is currently a fully cost-recovery-funded organisation, with the cost recovered from industry. Within the current funding model, an annual generic levy to fund drug information for prescribers and consumers could be considered. However, this would be less efficient than funding this work directly from taxes. The current TGA cost recovery funding model may be limiting its capacity to adapt and respond to quality issues use of medicines issues in Australia. It is time to change, the current PI of generic drugs are not fit for purpose and the current system is failing patients.

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LETTERS TO THE EDITOR

Clinical-scientific note

Drug-induced photo-onycholysis: an often-neglected phenomenon

A healthy 22-year-old man presented with a 1-month history of spontaneous fingernail discoloration. The nails had changed from yellow to purplish-black in colour, associated with slight pain initially. Examination revealed distal onycholysis of all fingernails. Concave and ovoid areas of yellowish discoloration were present on the right and left second to fifth fingernails, respectively. The right second, third and fourth fingernails showed subungual haemorrhage, while splinter haemorrhages were evident on the left second, fourth and fifth fingernails (Figs 1,2). Toenails were unaffected. There was no rash elsewhere on his body.

Presence of a soft parasternal systolic murmur prompted the referring physician to order a two-dimensional echocardiogram on suspicion of an atrial myxoma or valvular defects causing peripheral emboli. This was normal. The patient later revealed that he had undergone 1 month of military training in Australia during the summer; during which he had taken oral doxycycline for treatment of facial acne. The nail changes occurred a week after his return.

A diagnosis of doxycycline-induced photo-onycholysis was made. The patient was expectantly managed. At follow up 3 months later, the nail changes had resolved.

Onycholysis refers to the separation of the nail plate from the nail bed. Drug-induced photo-onycholysis occurs immediately after intake or several weeks after cessation of the offending drug. It may follow a photosensitivity reaction in the skin, or it can occur as the sole manifestation of a drug-induced phototoxic reaction, in the absence of cutaneous features.1–3 The convexity of the nail structure acting as a lens to focus ultraviolet radiation (UV) on the nail bed, the sparsity of melanin and absence of sebaceous glands in the nail bed are possible explanations for the predilection of photodamage in the nail. However, phototoxic changes may be demonstrated in clinically unaffected skin. In a patient who developed isolated onycholysis following doxycycline treatment, direct immunofluorescence of clinically normal sun-exposed skin revealed porphyria-like fluorescence with immunoglobulin M and immunoglobulin G deposition around papillary blood vessels.2

It is unclear whether UVA or UVB triggers the phototoxic reaction of drug-induced photo-onycholysis.2,5 Photosensitisation likely occurs only after prolonged and intense exposure to sunlight. Onychodynia, as our patient experienced, may precede onycholysis by 1 to 4 weeks and has been described only in association with tetracyclines and psoralen with UVA.7 The role of terminal vessels, capillaries or glomus bodies has been postulated, but the cause remains unknown. Local nail bed haemorrhage accounts for the dark red colour of the nails. Splinter haemorrhage occurrence has been reported in photo-onycholysis associated with
tetracyclines.\textsuperscript{6} Unawareness of this phenomenon may result in unnecessary investigations to rule out cardiac pathologies.

Despite the common use of doxycycline in medical practice, the occurrence of doxycycline-induced photoonycholysis is uncommon. It has been reported in the treatment of Lyme disease,\textsuperscript{3} malaria,\textsuperscript{7} respiratory tract infections,\textsuperscript{8} acne and acne rosacea.\textsuperscript{9} Gradual normalization of the nails occurs months after cessation of the drug. Drug reintroduction is not contraindicated, but advice against intensive sun exposure is important.

Less common causes of drug-induced photoonycholysis include chloramphenicol, oral contraceptives, chlorpromazine, thiazide diuretics and griseofulvin.\textsuperscript{10–12} Photoonycholysis occurs also in association with porphyria, pseudoporphyria and rarely as a spontaneous, isolated phenomenon.

In conclusion, we highlight that onycholysis may be the sole manifestation of a drug-induced photosensitive reaction, and awareness will aid physicians in prompt diagnosis.

\textbf{General correspondence}

\textbf{Doctor knowledge and attitudes to donation after cardiac death}

We would like to add our own experience to the report by Marck et al.\textsuperscript{1} In May 2013, we presented a poster on the historical and ethical aspects of the practice at the Royal Australasian College of Physicians Congress in Perth.\textsuperscript{2} We found only the occasional Fellow had heard the expression ‘donation after cardiac death’, and none knew it is related to a specific procedure, the aim of which is to enable organs to be removed as close to the instance of cessation of circulation as possible. First reported in 1993, the threshold decision is to allow the potential organ donor to die through termination of life support.\textsuperscript{3} When the organ procurement team is in place, circulatory failure is induced by removal of respiratory and other support. The calculation is that the hospital’s cessation of circulation criteria will be achieved within a set time, usually about 60 min from detachment. If the patient does not reach the cessation of circulation criteria within the required time, as occasionally happens, the procedure fails and the patient is moved to elsewhere in the hospital for palliative care. Many of our discussants expressed surprise that such protocols existed and some considered it euthanasia.
Author reply

We thank Michael and Judith Kennedy for their letter\(^1\) supporting our findings describing a lack of awareness and understanding of donation after cardiac death (DCD).\(^2\) DCD has been implemented in many hospitals around Australia guided by the DonateLife National Protocol for Donation after Cardiac Death,\(^3\) and 25% of the organs transplanted from deceased donors this year so far came from DCD donors.\(^4\) It is a concern that some physicians felt that DCD equated to euthanasia. This may reflect a lack of understanding about the process of withdrawal of life sustaining therapies in the intensive care unit (ICU). In Australia, DCD only occurs in the controlled setting in the ICU when the senior medical staff have determined that recovery is not possible based on a patient’s diagnosis, progress and known life wishes. Once the family has accepted the inevitability of death, an opportunity then exists to consider organ and tissue donation as part of end of life planning. The only influence organ and tissue donation has on the decision about a patient’s care is on the timing of withdrawal of life supporting treatments if donation is proceeding.

While many physicians will never encounter the reality of DCD, we feel it is important that all doctors have knowledge of the concept so they can have informed discussions with patients and their families and, if able to do so, express support for the processes around organ and tissue donation. This is of particular relevance to emergency physicians who are frequently faced with end-of-life decisions and should consider the possibility of DCD before withdrawal of treatment. The authors hope that a time will come when discussions around donation are a standard part of end-of-life care, that families will expect to be informed of their choices in this respect and that their treating physicians are able to provide them with accurate information.

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Letters to the Editor
Consider ceasing tenofovir in patients with proteinuria prior to nephrology review

Gracey et al. have made a significant contribution by highlighting the importance of screening for renal disease in patients with human immunodeficiency virus (HIV) as this common condition has been associated with increased mortality. Importantly, proteinuria per se has been demonstrated to predict mortality in patients with treated and untreated HIV infection. In the absence of nationally approved guidelines, Queensland HIV clinicians developed a statewide clinical guidance algorithm for the screening and management of proteinuria in patients with HIV. This algorithm has been widely implemented with almost 70% of patients with HIV in Queensland having a proteinuria screen in 2010.

The Queensland clinical guidance algorithm is similar to that proposed by Gracey et al. for the screening for renal disease. However, there is a significant difference in the approach to management of this condition. We agree with Gracey et al. that patients with HIV experience a high prevalence of renal risk factors; however, we suggest that a common modifiable cause of renal dysfunction in patients with HIV is antiretroviral therapy. Gracey et al. correctly acknowledges that tenofovir, the most commonly prescribed antiretroviral agent, and other antiretroviral agents are associated with renal disease. The prevalence of tenofovir-associated nephrotoxicity may be greater than that reported in Gracey et al.’s report, especially if proteinuria is taken into account. Randomised controlled trials (RCT) of tenofovir have not demonstrated significant nephrotoxicity; however, it is important to observe that most RCT have not examined the incidence of proteinuria and the duration of follow up has been short. Thus RCT are likely to underestimate the incidence of tenofovir-associated nephrotoxicity. Large observational studies demonstrate that tenofovir is associated with nephrotoxicity with an annual incidence ratio of 19% if estimated glomerular filtration rate (eGFR) alone is analysed but 34% if both eGFR and proteinuria are analysed. Local research suggests that tenofovir-associated nephrotoxicity may be reversible. Eleven of 12 patients who ceased tenofovir because of proteinuria experienced resolution of proteinuria within 6 months. Not all studies have demonstrated complete reversibility of tenofovir-associated nephrotoxicity. Patients in these studies were more likely to have ceased tenofovir because of falling eGFR rather than isolated proteinuria. It is therefore interesting to speculate that proteinuria may be an early and reversible manifestation of tenofovir-associated nephropathy that may predate significant eGFR decline. Ongoing studies are likely to elucidate the temporal features of tenofovir-associated nephrotoxicity.

In the absence of controlled clinical trial data, it seems reasonable that HIV clinicians consider cessation of tenofovir in patients with proteinuria who have no other obvious cause of proteinuria such as hypertension or diabetes. In some situations, the clinical risk of tenofovir cessation may outweigh the potential benefit of reducing risk of nephrotoxicity. Experienced HIV clinicians are capable of making decisions regarding the safety of tenofovir cessation and balancing risks. Cessing tenofovir in patients with otherwise unexplained proteinuria prior to nephrology referral may be a more prudent approach than overloading already stretched renal outpatient departments. Patients in whom proteinuria persists despite tenofovir cessation should be referred for nephrology review.

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Letters to the Editor

Author reply

We welcome the comments by Kelly et al.1 regarding our recent article highlighting the importance of screening for renal disease among Australian patients infected with human immunodeficiency virus (HIV).2 It is clear that there is a disproportionately high burden of renal disease observed in this patient population, which is likely to increase and is presently under recognised.3 This is also highlighted by Kelly et al. in their review of the measurement of proteinuria as a key performance indicator in Queensland HIV clinics in 2010;4 less than 70% of all patients had been screened for proteinuria in that year. It is not clear what method was used by the participating clinics to screen for proteinuria; it is also not clear if these patients were also screened for clinical risk factors of renal disease and had an estimate of their renal function performed (estimated glomerular filtration rate (eGFR)). International guidelines suggest that every newly diagnosed patient should be screened for renal disease at baseline, or at commencement of antiretroviral therapy, and then at least annually; more frequently if they are considered at high risk of renal disease.3

HIV infection itself is known to be associated with the abnormal excretion of urinary proteins.5 Importantly, in many HIV-infected patients, increased albuminuria or the urinary excretion of other proteins may be found in the absence of intrinsic renal disease and may be a non-specific finding, possibly relating to immune abnormalities. This phenomenon is observed in both treatment of naive and experienced patients. Data from the general population also demonstrate that albuminuria is a sensitive and early predictor of cardiovascular risk, even in the absence of existing renal disease.6

Given these data, we would recommend a complete assessment of any patient found to have proteinuria before any decisions are made regarding modifying their antiretroviral therapy. We would recommend a confirmatory sample with a quantification of the amount of proteinuria, using a spot urinary protein : creatinine ratio. Some patients may have false positive urinary protein tests, particularly in the presence of a febrile illness, urinary tract infection or sexually transmissible disease.6 As well, there may be identifiable and reversible causes of proteinuria, such as excessive exercise or the use of other medications such as non-steroidal anti-inflammatories. In choosing antiretrovirals, the patient’s renal function should be considered, as well as degree of proteinuria and an individual’s clinical risk factors for renal disease. Patients should be referred to a renal physician if they have significant proteinuria, persistent microhaematuria or chronic renal impairment (eGFR < 60). Patients with a rapidly declining eGFR, which is still above 60, should also be considered for referral. For many, potentially nephrotoxic antiretrovirals may still be safe and effective options, providing that guidelines for screening of renal toxicities are followed.

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Private hospitals and physician education

Tiong et al. have endeavoured admirably in addressing the perception that students on placement in private hospitals are disadvantaged. In fact, it seems to us that they have underinterpreted the data in their study. The demographic differences they have identified may actually also explain why patients in private hospitals are relatively amenable to medical student participation in interviews and procedures.

Two important participant characteristics may help further explain the findings of the study. First, patients at private hospitals have, on average, a higher educational attainment. Thus, one would expect them to be more sympathetic to the needs of students as they were once students themselves. Second, they have collectively had fewer medical student encounters previously. If they had seen more students previously, as was the case with their public hospital counterparts, they may be less receptive to student involvement. Hence, on both counts, students on placement in private hospitals stand to benefit.

Extrapolating to the theme of Amos et al. that clinical exposure in specialty training has declined over recent years as an inevitable parallel of the increasing number of trainees, the possibility of involving private hospitals with training programmes seems very attractive. However, private health organisations may be reluctant initially. As pointed out in the article, they work as fee-for-service entities, and their primary objective is to ‘keep the customers happy’. However, contrary to another misconception, patients in private hospitals are often quite willing to contribute to medical education. If they are (as a whole) agreeable to medical student interviews, then logic would suggest they are equally (if not more) likely to be agreeable to having input into the experiences of a trainee specialist. In fact, a major conclusion of a study along these lines regarding urology training found private hospital patients to be very accepting of registrar participation if consultant involvement is emphasised. Likewise, registrars are generally well accepted in (private) general practice.

This approach would certainly help to address the exposure shortage of advanced physician trainees. It would also provide trainees with important insight into the differences between the clientele and issues of private practices and hospitals in comparison to the public system in which they have exclusively participated up to that point.

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training in the private hospital setting. 


Author reply

We thank Lee and Baer\(^1\) for highlighting the benefits of increasing private hospital participation at all levels of medical training. They raise an interesting point that differences in patient characteristics may help to explain the willingness of some patients to participate in medical training. Admittedly, our study\(^2\) was not designed nor powered to perform this level of multivariate analysis. Our focus was instead on the overall proportions of patients in each setting that would consent to seeing students during the course of their care. We reasoned that it was these overall proportions that were important to answer the question whether students placed in private hospitals could expect to be disadvantaged by reduced access to patients.

However, certainly from our personal experience (as a medical student and clinicians), it would appear that overexposure to trainees may negatively impact on some patients’ receptiveness towards students. Public hospitals are not only the training ground for the majority of medical students and junior doctors, but also for nursing and the allied health disciplines. From our experience, this understandably leads to ‘student fatigue’ among some public hospital patients who might otherwise be obliging participants.

The suggestion that higher education may make a patient more sympathetic to the needs of medical students is interesting. While this is logical, previous studies have suggested that the effect of education is minimal if present at all.\(^3\)–\(^6\) Less formal education does not appear to preclude a patient from seeing the value of participating in the education of Australia’s future doctors. The above studies and our own data suggest that irrespective of patient characteristics, there is a high level of support for participation in medical education.

We agree that our results could reasonably be extrapolated to more advanced trainees and hope that this encourages key stakeholders to utilise better the training opportunities that exist in private hospitals. We would also point out that private hospitals benefit from public funds, either through direct funding or through the service of clinicians who have been trained in the public system. Therefore, we would argue that even if private hospitals do not have a legislative obligation to participate in medical training, they still have a moral obligation to contribute to the ongoing sustainability and improvement of the Australian health care system.

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On-road driving assessment in dementia

Carmody and colleagues1 have written a balanced and logical approach to driving in dementia. I endorse their view that a blanket restriction on driving simply because of diagnosis of dementia is unwarranted until overwhelming evidence from road crashes supports this conclusion. I also agree that loss of driving licence has adverse personal, social and recreational consequences, particularly for people living in areas without good bus or train services or close proximity to shopping for groceries and other essentials and recreation such as restaurants or bowling clubs. Many elderly people who lived through the Great Depression of the 1930s regard taxis as for millionaires. Carmody’s article refers to health professionals such as physicians, occupational therapists, optometrists and physiotherapists reporting unsafe driving. It does not however discuss the role of occupational therapists and neuropsychologists to assess cognitive fitness for driving. None of the 45 references cited by Carmody mention psychology or occupational therapy in their titles nor are they from psychology or occupational therapy journals. I believe that the closest test to actual unsupervised driving is an on-road (supervised) driving assessment by an occupational therapist or other health professional. It does not however discuss the role of occupational therapists and neuropsychologists to assess cognitive fitness for driving. None of the 45 references cited by Carmody mention psychology or occupational therapy in their titles nor are they from psychology or occupational therapy journals.

I accept that performance anxiety may affect supervised driving performance as compared with unsupervised driving. On-road assessment using the patient’s vehicle has no capital costs. However, a dual control vehicle that allows the driving instructor to prevent accidents has additional capital costs. The next best alternative to on-road assessment is a driving simulator. Systems Technology Incorporated in Hawthorne California sells driving software from $6325 to simulators that cost $10 000 to $80 000. Their equipment is found in eight Australian universities (personal communication). I strongly doubt that driving simulators costing over $10 000 will disseminate outside of research centres. For example, for years, I have advocated at conferences and in research articles that the whisper test (no capital cost) should precede cognitive examination in older people. This has seldom been implemented. I further advocated that when the whisper test is impaired despite hearing aids, physicians use portable amplifiers with headphones (capital cost $240, consumables are a pair of AA batteries every 6 months). Uptake of this diagnostic aide remains low. I can offer one strategy that may add predictive power for patients with mild cognitive impairment or early dementia who are still driving. In the Wyong Hospital Memory Clinic, I assess patients with mild cognitive impairment or dementia every 6 months using several brief neuropsychological tests such as Montreal Cognitive Assessment, digit span, Frontal Assessment Battery and instrumental activities of daily living reported by family. I then calculate their mean cognitive trajectory for each test. I propose that a patient on a rapid downhill course (10–15% decline per year) is more likely to become an unsafe driver within a year than a patient declining 2% per year. This hypothesis would need to be examined against on road driving assessment.

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Reference

Author reply

We thank Regal1 for his interest and his kind comments regarding our paper.2 Our principal aim was to highlight several key ethical issues faced by Australian physicians (e.g. reporting obligations, negative consequences of driving cessation). Regal raises a challenging, yet unresolved, dilemma: which test best determines safe driving capacity? Although an in-depth appraisal of existing tests was beyond the scope of our paper, we did refer to two seminal reviews. The Australian and New Zealand Society of Geriatric Medicine (ANZSGM)3 and the American Academy of Neurology (AAN)4 have comprehensively reviewed the existing literature regarding assessment of fitness to drive of individuals with dementia. Neither organisation supports sole reliance upon occupational therapy assessments in determining driving safety. As quoted in our paper, the AAN systematic review concluded that ‘there is no test result or historical feature that accurately quantifies driving risk’.2,4 Additionally, in relation to driving simulators, the ANZSGM notes that ‘most evidence indicates that performance in driving simulators is not strongly related to on road driving performance’.3

In an attempt to ease the transition to driving retirement by individuals with dementia, we are currently testing a novel Decision Aid booklet in a randomised controlled trial (HREC 12/016) in Australia and New Zealand.5 It is hoped that this novel approach will assist drivers with dementia planning for driving retirement. Early discussion of this issue may negate the need for abrupt and potentially distressing licence withdrawal at a later date. Potential participants or interested clinicians are welcome to contact Dr Carmody (+61 2 4253 4430 or john.carmody@sesiahs.health.nsw.gov.au) to enrol or learn more.

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Letters to the Editor

A significant gap still exists between clinical guidelines and practice for hip and knee arthroplasty

We read with interest and concern Mirkazemi et al.'s article on the low rate of venous thromboembolism (VTE) prophylaxis (36.5%) utilised in patients following discharge after an elective hip or knee arthroplasty. The retrospective data presented from 300 consecutive patients during 2007–2009 showed that almost all patients (98.4%) adhered to most guidelines advocating VTE prophylaxis, and stressed the importance of a need for further research.

As part of the Elective Joint Replacement Working Party of the Agency of Clinical Innovation (ACI)’s Musculoskeletal Network, NSW Department of Health, we undertook an extensive evidence-based review, including eight relevant papers and five clinical guidelines with recommendations based on different clinical end-points, and three systematic reviews. Our recommendations (Grade A, National Health and Medical Research Council (NHMRC)) were that ‘a multimodal approach to VTE prevention, initiated in the preoperative period and continued after discharge from acute care. Pharmacological modalities include low-molecular weight heparin, Fondaparinux, Aspirin, Rivaroxaban or Dabigatran, supplemented by the use of physical devices and early mobilisation’. For pharmacological modalities, the pharmaceutical benefits scheme currently advocates 14 days following an elective total knee and 28 days following an elective total hip replacement.

We note that while Mirkazemi et al. reported guidelines from Australian and New Zealand Working Party, American College of Chest Physicians (ACCP), American Academy of Orthopaedic Surgeons (AAOS) and Arthroplasty Society of Australia between the periods 2004 and 2007, there are updated guidelines for the ACCP (2008), AAOS (2009), NHMRC (2009), National Institute for Health and Clinical Excellence (2010), Scottish Intercollegiate Guidelines Network (2010) and the Cochrane Collaboration (2008, 2010).

One reason for which there are low patient adherence rates following discharge in this patient cohort in Tasmania may be that clinicians and pharmacists had not yet updated their guidelines. We advocate that clinical guidelines, such as the ACI’s, be widely disseminated and incorporated into local guidelines, and that these are updated annually or biennially to incorporate new evidence. Perhaps with increased adherence to such guidelines we can achieve a better VTE complication rate.

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Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. 

Cochrane Database Syst Rev 2008; CD005258.


Cochrane Database Syst Rev 2010; CD001484.
aims and scope
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