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Internal Medicine Journal

Volume 43, Issue 4, April 2013, Pages 351-472

ISSN 1444-0903

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Almost no one wants to be and/or enjoys being unwell or injured. For most, visits to doctors and other health providers, and especially to hospitals, are associated with unpleasant feelings and usually some anxiety. This ‘distress’ is often rooted in quite strongly held illness-beliefs about cause, symptoms, duration and outcome.1 These beliefs in turn are frequently the outcome of direct and indirect personal experience, religion, sex and culture, and are influenced by friends, family and the ‘media’. Lay consumers of healthcare are also increasingly informed, if not always well informed. This ‘information’ is assimilated into and influences belief systems and consequent ‘help-seeking behaviours’.1 Although communication between healthcare providers and consumers in this milieu is complex and demanding, there is an opportunity to improve the wellness of our communities through better health literacy2,3 and consequently to help address the demands of patients with worrying health outcomes. At the other extreme, and perhaps just as disadvantageous, is the extremely health literate sick or injured health provider – our attention here is on the unwell doctor.

There are many expert ‘sick doctor schemes’ in place, and most have the dual role of ensuring patient safety and doctor well-being.4,5 The order of this obligation is probably appropriate. Our intent is not to review these schemes but, rather, to consider how we look after each other on a day-to-day basis and for problems that are almost always short of the threshold of notifying medical councils or boards, and employers. It is also to consider how well we are prepared to engage as a ‘patient’ so that the care we receive can be as effective as is possible.

The first question then is provider-centric and is how well do we do in our day-to-day practice when one of our colleagues comes to see us with a health problem or injury, or we encounter them in their role as a doctor and them as a patient? Given the recent experience of the more ‘aged’ of us, during a recent hospital admission and related consultations, the answer is variably very well.

None of our lay patients is as well informed as our medical patients. That ‘insight’ and knowledge might present as a challenge to our assessment, diagnosis and treatment. An a priori self-diagnosis is probably inevitable and will vary from catastrophic to dismissive. The clinical history given to us then is consequently possibly both edited and biased, and predestined to achieve or predicate on a particular outcome. Deep fears might suppress information; clearly, all of these phenomena can and do exist in any sick or injured person, but in our experience, doctors are more likely to manifest these traits and to the extreme.

The challenge then is to accommodate this so well-informed patient in a way that does not cause you to deviate from your usual best practice. A sick doctor does not deserve or warrant an abbreviated or presumptive interview; possibly, embarrassing questions need address. If the unwell doctor is unable to engage you in such a way, you are probably not the best person to be seeing them. Your hypotheses need to be tested clinically as you would otherwise do so, as the predictive power of examinations and investigations does not change according to the profession of the patient. Similarly, informed consent in regard to ‘tests’ is essential, and this must encompass conversations about absolute risk, how they and you will react to certain test outcomes, and so on. ‘Fishing expeditions’ are frequently complicated by perverse outcomes and perhaps even more so in this context. Second opinions are usually not a sign of weakness. Every patient needs your holistic care; your colleague is no exception and is very likely to be far more anxious than is apparent.

The discussion of treatment options is another aspect of the engagement that requires careful behaviour. You are not two colleagues talking about how to treat someone else. You are a doctor talking to a colleague who is unwell and who is seeing you in the capacity of a patient. The conversation must be subjective. We find it helpful to involve ‘significant others’, and their collateral history is also invariably valuable. Do not be reticent to talk about their mental health, which should include everything from their fears and feelings, and expectations, to how they are sleeping, eating and working. Notification of medical regulators and employers might need to be brought up; early and voluntary notification, if appropriate, is usually much better for everyone.

Similarly, follow up should be as your usual practice; over-zealous oversight may likely exaggerate already-profound anxiety, and being too discretionary and lax on the basis that the medical patient has insight and will inevitably come back if something is amiss is equally poor practice.

In our opinion, developing and maintaining these skills and practices need to be part of our routine continuing
medical education and professional development. We also need to think about how we should behave and engage with our colleagues when we are the unwell person.

In the context of the latter, it is not easy to make the transition from doctor to patient from any viewpoint. A medical friend and colleague describes this a profound gearshift and especially so when the clinical situation is uncertain, or tests results or responses to treatment are awaited.

For some of us, this shift will predominantly be a problem of surrendering ‘command and control’ and accepting a shared decision-making role with our health providers. As an aside, a good general medical practitioner is almost always the best first person of contact and especially if the problem is not well differentiated with respect to cause.

Many of us will find it an even greater struggle to change roles when the person we are consulting is otherwise a relative or friend, or former student.

We are strong believers in mentors and are grateful for the people who have mentored us. It is very helpful to have someone you can talk to about your emotions and thoughts. This is not an argument against early consultation with mental healthcare providers but is one of the ways in which we can prepare ourselves for being unwell and to help us behave in a way, when we are unwell, that positively contributes to a good outcome.

George Burns is famously quoted as saying that ‘sincerity is everything, when you can fake that you’ve got it made’; putting aside his ironic humour, honesty is everything. If you cannot confide without reservation with the person you are consulting, then see someone else. Try to describe your symptoms as such, and so on, and try to avoid, if possible, confronting the person you are seeing with your chosen self-diagnosis. Your differential diagnoses might be better seen as your desperate hope at one extreme and/or your worst nightmare at the other. If you can and the problem is really troubling you, take someone with you so that a more objective account of just what was and was not said is available to you afterwards, and to enable a collateral history. If possible, leave your ego at the door as this is not a competition or a popularity contest.

If you are worried, you are worried and reassurance is something you deserve, assuming that some is possible. Knowledge of something ‘bad’ is a better situation for most of us than not knowing. It helps to know your ‘personality style’ in this context and to ensure that the person you are seeing is explicitly aware of this, which is another of the many advantages of a regular general practitioner.

When dealing with a ‘threat’, such as a health issue, many of us adopt one of two ‘coping’ styles, and this is rooted in personality psychology. Many are described as ‘monitors’. Such people have an insatiable appetite for information and cope well only when given large amounts of information. In turn, ‘monitors’ have been shown to be more ‘demanding’ patients and often ‘want-more’ out of their physician. If the person you have chosen to see is irritated by your pursuit of information and consequent reassurance, then you have chosen badly and should try someone else.

Others are labelled as ‘blunters’. This type of person seeks and is happy with general and strategic reassurance about the nature of the problem, and the relative expertise and appropriateness of the provider and any treatment. Detailed information to those who blunt is distressing and progressively so.

It is incumbent on all of us in the health professions to look after each other and that will require appropriate professional behaviour whether we are engaged as a provider or consumer. We have an obligation to our colleagues and, in order to serve our communities, to our own wellness. There are underpinning skills to this end that need to be established and maintained.

Received 5 February 2013; accepted 6 February 2013.

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References
REVIEW

Recent advances in the management of transient ischaemic attack: a clinical review

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Key words
TIA, carotid, atrial fibrillation, organisation.

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Received 24 August 2012; accepted 14 December 2012.
doi:10.1111/imj.12059

Abstract
Transient ischaemic attack (TIA) if untreated carries a high risk of early stroke and is associated with poorer long-term survival. There have been recent advances in the understanding of TIA, its investigations, management and organisation of services for patient care. Clinically, patients are diagnosed TIA if they have transient sudden-onset focal neurological symptoms which usually completely and rapidly resolve by presentation. Patients with residual symptoms should be evaluated as potentially having stroke, if they present within 4.5 h of onset, should be urgently evaluated for their potential eligibility for thrombolysis. TIA patients should receive rapid attention with essential investigations, including brain imaging, electrocardiograph and carotid ultrasound. Immediate administration of an antiplatelet agent is recommended after brain imaging, with subsequent attention to preventing or treating other mechanistic factors. There is emerging evidence that TIA patients can be managed safely in the outpatient setting after initial rapid management in emergency departments as part of a structured clinical pathway supervised by stroke specialists. Clinical systems of management may require approaches individualised to the healthcare setting, while adopting the central aspects of rapid management.

Introduction

Transient ischaemic attack (TIA) is a significant public health problem. Despite knowledge on the incidence of stroke in Australia,1 the true incidence of TIA in the Australian community remains poorly understood. The long-term survival after TIA in Australia is reduced by 4% at 1 year and 20% at 9 years relative to the general population, with age, prior stroke and cardiac disease being the main explanatory factors.2 TIA heralds the onset of stroke in about 10%3 in untreated cases, and thus remains an extremely important condition to diagnose and treat. With appropriate accelerated evaluation and treatment, post-TIA stroke rates can be as low as 1–3% at 90 days.1,3

Differentiation between TIA and stroke
The duration of symptoms is important with respect to differentiating between TIA and stroke4 (Box 1). The basis for the 24-h threshold for definition of TIA comes from the pre-imaging era (circa 1965). However, the selection of this threshold was arbitrary, as subsequent observational studies indicated that the duration of a ‘true’ TIA may be in the order of minutes (approximately...
5 to 10 min) and usually less than 60 min.\(^7\) These findings are in keeping with diffusion-weighted magnetic resonance (MR) studies (DWI) showing ischaemic changes in 30% of patients with symptoms of \(\leq 1\) h duration and 51.1% of patients with symptoms > 6 h. Consequently, there is emerging support for the use of a tissue (DWI)-based diagnosis of TIA over the time-based definition.\(^6\) The American Heart Association recently endorsed the following definition of TIA ‘a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, \textit{without acute infarction}'. However, it would not be justifiable or feasible to perform acute MR imaging in all TIA patients. Advanced imaging may be justifiable in patients who have evolving symptoms or ‘improving’ neurological deficits. In these patients, distinguishing between TIA and stroke is crucial, as the presence of the latter may be an indication for thrombolysis. We illustrate this in Figure 1 in the case of a patient with improving neurological deficit who was found to have major cerebral arterial occlusion that recanalised following thrombolysis. Recognising that patients with apparently ‘improving’ symptoms may be mistaken for TIA, we characterise TIA patients as having symptoms (heard) but no signs (not seen) by the time they present to hospital. In other words, patients with neurological signs at presentation should be evaluated as stroke.

### Clinical features

The clinical features of TIA are those caused by ischaemia affecting eloquent brain areas. Features compatible with anterior circulation TIA commonly include unilateral motor, sensory or sensorimotor impairment, dysphasia and amaurosis fugax. A history of dysphasia provides lateralising information that helps with inference on the carotid artery territory. The diagnosis of amaurosis fugax is based on the patient’s report of a transient unilateral visual loss, described on closer questioning as ‘a curtain coming down’ over the affected eye with inability to see through this curtain. Neglect is usually not encountered in ‘true’ TIA probably because it is also determined by

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**Box 1 Take-home messages**

- TIA patients have transient focal neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, \textit{without acute infarction}.
- TIA symptoms are brief in duration (< 60 min).
- TIA may be characterised as ‘heard’ (symptoms) but not ‘seen’ (no signs).
- Essential tests: CT scan, ultrasound, ECG.
- Immediate therapy: antiplatelet drugs
- Stroke mechanisms requiring urgent attention: carotid artery stenosis and atrial fibrillation.
- Outpatient management can be performed safely in the setting of structured TIA pathway.
- Secondary prevention strategy important in stroke prevention.

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\(\text{Figure 1}\) This 70-year-old male patient presented within 2 h of symptoms onset. He had patent foramen ovale closure performed 3 years prior. He was noted to have rapidly improving left-sided weakness but persistent neglect. The computed tomography (CT) angiography study showed occluded right middle cerebral artery (blue arrow). He was given tissue plasminogen activator with good effect and was discharged from hospital after 2 days. Magnetic resonance (MR) imaging study showed recanalisation of the right middle cerebral artery and infarction involving the striatocapsular region and the right superior temporal gyrus (red arrow). DWI, diffusion-weighted MR studies.
clinical examination rather than being expressed as a symptom. Features of posterior circulation TIA include vertigo and/or diplopia, or loss of balance, or unilateral weakness. In the context of sudden onset of visual symptoms, it is important also to check for the presence of a hemianopia from ischaemia of the visual cortex, and its presence should alert the clinician to the possibility that a stroke has occurred. Uncommonly, some patients with chronic occlusion or near occlusion of the carotid artery may complain of loss of vision in the presence of seeing ‘bright lights’ from retinal ischaemia, or give a history of contralateral limb shaking mimicking seizures but without epileptiform activity on electroencephalography.

**TIA mimics**

Several conditions may often be associated with symptoms similar to those seen in TIA, and are referred to as ‘TIA mimics’ (Table 1). Australian data suggest that TIA mimics account for around 22–38% of patients with suspected TIA.8,9 Patients with complex migraine may describe visual blurring, positive visual phenomena in the hemifield or a gradual ‘march’ of sensorimotor symptoms. Headache in these patients may not be prominent at the time of hospital presentation and hence this diagnosis may not be considered. The clue here is that these patients are more often young and female. Vertigo occurring on its own, rather than in conjunction with other brainstem features such as diplopia and dysarthria, is often due to a peripheral vestibular cause. An altered conscious state may occur in hypoglycaemia and other medical (arrhythmia, pulmonary embolism) or neurological conditions (seizure), but generally not in TIA. The high prevalence of TIA mimics has led to proposals for the application of diagnostic tools, such as Recognition of Stroke in the Emergency Room scale (clinical features, absence of hypoglycaemia, syncope and seizure), to assist in diagnosis. When this scale was independently evaluated, it had a low positive likelihood ratio (1.48) and negative likelihood ratio of 0.38,10 suggesting that it is not a useful clinical tool for differentiating between TIA/stroke and mimics. Given the spectrum of TIA mimics, specialist review is required for accurate diagnosis. In the TIA clinics conducted in our centre, this is achieved by stroke neurologists working in tandem with a stroke specialist with expertise in neurology.3 In other rapid TIA pathways, the clinics are either conducted by neurologists3 or ‘vascular’ neurologists.4

<table>
<thead>
<tr>
<th>Causes</th>
<th>Frequency (n = 187)</th>
</tr>
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<tbody>
<tr>
<td>Migraine</td>
<td>66 (35.3%)</td>
</tr>
<tr>
<td>Peripheral vertebulopathy</td>
<td>22 (11.8%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>14 (7.5%)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>13 (6.9%)</td>
</tr>
<tr>
<td>Stress/anxiety</td>
<td>13 (6.9%)</td>
</tr>
<tr>
<td>Transient global amnesia</td>
<td>10 (5.4%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>7 (3.7%)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>40 (21.4%)</td>
</tr>
</tbody>
</table>

**Risk stratification and prognostic tools in TIA**

There is intense interest in risk stratification of TIA patients to identify who may be at high risk of future stroke, to allow prioritisation of specific investigations, treatments and even triage admission to hospital. The most popular risk stratification tool has been the Age, Blood pressure, Clinical features, Duration and Diabetes (ABCD2) score. A previous meta-analysis11 showed that the area under the curve for recurrent stroke at 7 days using the ABCD2 score was 0.70, suggesting a 30% probability of incorrect classification. Data from two recent Australian studies have shown that this tool has low predictive value for stroke recurrence in tertiary settings.8,12 Taken together, these findings show that the scale does not reach the required threshold for appropriate urgent clinical decision-making about urgency of investigations and admission. Others have tried to improve its accuracy by adding imaging findings, carotid artery stenosis and atrial fibrillation (AF) to the scale, but the value of even this revised tool is uncertain because its accuracy in validation samples was not superior to the original ABCD2 score.13 At the present time, such scores cannot replace or enhance clinical expertise directed at urgent identification of modifiable underlying vascular mechanism (carotid stenosis, AF) and prompt commencement of antiplatelet or anticoagulant therapy.

**The role of brain imaging**

Brain tumour, subdural haematoma and convexity subarachnoid haemorrhage can all mimic a TIA (see case vignette in Fig. 2). Consequently, urgent brain imaging is required to exclude these lesions before administering antiplatelet therapy. To enable such evaluation, it is ideal if patients with suspected TIA are evaluated rapidly in a hospital emergency department with access to physician expertise in stroke neurology and radiology. It should be cautioned that a normal brain scan does not exclude a diagnosis of TIA.

Some TIA patients, whose symptoms resolve rapidly, may delay seeking medical attention. Outpatient imaging of such patients may be appropriate if there is access to urgent specialist attention and rapid conduct of addi-
tional relevant imaging and other investigations, as there is urgency in deciding on appropriate secondary prevention strategies. A system for outpatient investigations may be facilitated by physical co-location of the consulting suites and radiology services to enable instant communication of test results between clinicians and radiologists.

**Other investigations**

The priority and choice of other investigations in TIA is driven by the need for treatments based on the strength of underlying clinical trial evidence. Importantly, large artery disease (symptomatic critical carotid artery stenosis) and AF are two stroke mechanisms that require specific and urgent treatments that have proven efficacy, namely carotid endarterectomy and anticoagulation respectively.

Carotid ultrasound should be performed within 24 h to facilitate planning for carotid revascularisation (timing of surgery will be discussed under Carotid Revascularisation). The ultrasound threshold for triggering confirmatory studies such as computed tomography (CT)/MR angiography at our centre is 50% carotid artery stenosis, to avoid missing cases of ≥70% stenosis that may get misclassified as 50–70% stenosis on ultrasound. Recent advances in CT/MR angiography has meant that digital subtraction angiography is now rarely used. In our centre and in keeping with evidence, we generally do not operate on patients with moderate stenosis because the benefit is relatively small. However, we do offer surgery in certain high-risk situations, such as moderate stenosis in the presence of an ulcerated plaque. While interpreting carotid imaging findings, clinicians should look at two key issues: (i) Is the diseased artery responsible for the stroke and does this patient require carotid revascularisation? This is the case when there is stenosis of the internal carotid artery ≥70% ipsilateral to the affected cerebral hemisphere; (ii) If the carotid artery is diseased but the stenosis is <70%, can that artery be responsible for the stroke? This requires examination of the Doppler velocity and waveform profile as well as the B-mode (greyscale) ultrasound. The absence of any plaque suggests that the artery is less likely to be responsible for the ischaemic event.

Detection of a cardioembolic mechanism is important, with excellent evidence supporting a role for anticoagulation in preventing recurrent stroke in the setting of AF. Apart from clinical examination for an irregularly irregular pulse, the electrocardiograph (ECG) is an essential tool to diagnose AF. An abnormal P wave morphology and prolonged PR interval (>200 ms) on the ECG may be a pointer to abnormal atrium and presence of AF. The chances of detecting AF may increase with more prolonged monitoring with outpatient-based procedures such as Holter or loop cardiac monitors. Prolonged monitoring to detect AF may particularly be indicated in those with echocardiographic evidence of an enlarged left atrium or rheumatic mitral valve disease.

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The finding of patent foramen ovale (PFO) on echocardiography should be cautiously interpreted in the clinical context (Fig. 1 and brief case vignette). The results of the recent PFO closure trial showed that closure of PFO was not superior to medical therapy and was associated with a 10-fold increase in the risk of AF. The use of transoesophageal echocardiography specifically to detect aortic arch atheroma has not been emphasised here because it does not result in a change in medical management. This position may change once the result of the aortic arch disease trial is announced (http://clinicaltrials.gov/ct2/show/NCT00235248, accessed 31 October 2012).

In the evaluation of patients with TIA, it is more important first to evaluate prevalent and modifiable
biochemical risk factors for stroke, such as blood glucose and lipid profile, rather than to screen routinely for thrombophilia and vasculitis which are extremely infrequently associated with stroke. The prevalence of any inherited thrombophilia in stroke patients was found to be similar to stroke-free controls (14.7% vs 11.7%, P > 0.4). Recurrent stroke occurred in 22.2% of patients with anticardiolipin antibodies and or lupus anticoagulant similar to 21.8% in those negative for these antibodies. Aspirin is as effective as warfarin for preventing stroke recurrence in these patients. There are other potential stroke mechanisms which are far less common, and these are best looked for in specialist settings.

Secondary prevention

**Antiplatelets**

Aspirin has proven efficacy for secondary ischaemic stroke prevention. Recent trials have shown that the combination of low-dose aspirin and dipyridamole was superior to aspirin, with a similar effect as clopidogrel for prevention of recurrent stroke. The difference in outcome between phase 1 (antiplatelet drugs not given immediately, 10.3% stroke recurrence) and phase 2 (antiplatelet drugs given immediately, 2.1% stroke recurrence) of the EXPRESS study demonstrates the importance of commencing antiplatelet drugs immediately after brain imaging. There is no advantage in combining aspirin and clopidogrel in the subacute and chronic phase of TIA/stroke as this combination is associated with higher-than-expected frequency of haemorrhage. The efficacy of this combination (clopidogrel and aspirin) in acute TIA/stroke will be tested in a new trial (http://clinicaltrials.gov/ct2/show/NCT00991029, accessed 31 October 2012). Cilostazol is a new antiplatelet agent on the market in Japan (not yet listed in Australia) and proven to be effective for stroke prevention. Other agents (e.g. Ticagrelor) used in cardiological practice are yet to be tested for stroke prevention.

**Anticoagulation**

The effectiveness of warfarin for primary and secondary prevention of AF has been established. The efficacy of warfarin in the elderly (>75 year old) is supported by a British trial targeting this age group. Warfarin was superior to combined clopidogrel and aspirin in preventing recurrent stroke and with surprisingly less intracranial haemorrhage events. Despite this evidence, warfarin is still underutilised for fear of causing harm (intracranial haemorrhage). The arrival of the newer anticoagulants, such as dabigatran, rivaroxaban and apixaban, may encourage the use of anticoagulants due to the absence of requirement for regular blood tests and reduction in risk of intracranial haemorrhage. Interventions such as the use of the atrial appendage occluder device may also be superseded by the arrival of the newer anticoagulants. A possible role for this device is in patients in whom anticoagulants are contraindicated, such as coexisting intracranial haemorrhage.

**Antihypertensive medications, statins and vitamin supplements**

Trials of antihypertensive therapy (perindopril) and statins (Atorvastatin) have clearly shown that their use can reduce recurrent stroke. The combination of angiotensin-converting enzyme inhibitor (ramipril) and angiotensin receptor blocker (telmisartan) did not provide additional benefit over either agent alone but may result in increased frequency of hypotension, syncope and renal dysfunction. Blood pressure reducing drugs are still underutilised, and Australian investigators are evaluating organised primary care approaches using Federal primary care initiatives (e.g. new Medicare reimbursement items) to improve implementation of the use of these drugs. It should be recognised that there are some circumstances where it may not be desirable to lower blood pressure aggressively, such as in patients with complete or near-complete occlusive carotid artery disease and clinical judgment is important. Although statins have proven efficacy in stroke prevention, there are some concerns regarding their use for fear of a risk of diabetes. In a reanalysis of a primary prevention trial with rosvastatin, this risk was observed in patients with impaired fasting glucose rather than those with normal glucose profile. So far, we have not discussed the optimal glucose control for (type 2) diabetic patients with TIA. This has come about because the results of recent trials in diabetic patients to reduce cardiovascular complications remain controversial. The recent review advocates a more individualised approach in the elderly patients to glycaemic control related to the patient’s long term survival and presence of multiple comorbidities and cognitive impairment. The promise of multivitamin, vitamin B, C and selenium and omega 3 fatty acid supplements have not been borne out. Vitamin A, \( \beta \)-carotene and E may be harmful and thus cannot be routinely recommended.

**Lifestyle risk factor modification**

Lifestyle risk factor modification (smoking cessation, reducing salt intake, healthy eating (fruit, nuts, reduced red meat, increased fish consumption (not fish oil) and exercise) is an important part of secondary stroke prevention.
prevention. However, it is not certain how these programmes should be developed. For example, should these be delivered at the time of clinic consultation or in conjunction with a lifestyle programme? Using Markov modelling for primary prevention in the Australian setting, investigators argued that ‘lifestyle interventions aiming to change risky dietary and exercise behaviours are extremely poor value for money and have little population health benefit.” Further work in secondary prevention in TIA and stroke patients is needed to determine the optimal method and cost-effectiveness of lifestyle interventions.

**Carotid revascularisation**

The benefit of carotid endarterectomy for symptomatic severe carotid stenosis has been established. Recent data from the Swedish vascular registry suggested that endarterectomy combined with mortality and stroke within 2 days of ischaemic event was 11.5% compared with 3.6% at day 3. In our centre, we prefer this policy within 2 days of ischaemic event was 11.5% compared to best medical therapy in the Stenting and Aggressive Medical Management for Prevention of Recurrent stroke Intracranial Stenosis trial. The 30-day rate of stroke or death in that trial was significantly higher in the stenting group (14.7%) than in the medical management group (5.8%).

**Intracranial stenosis**

The optimal medical treatment for TIA in the setting of symptomatic intracranial stenosis is less certain. Warfarin was not better than aspirin in this setting, while the role of combined aspirin and clopidogrel is uncertain. By contrast, stenting of the intracranial arteries was not superior to best medical therapy in the Stenting and Aggressive Medical Management for Prevention of Recurrent stroke Intracranial Stenosis trial. The 30-day rate of stroke or death in that trial was significantly higher in the stenting group (14.7%) than in the medical management group (5.8%).

**Organisation of services**

In the earlier sections, we have briefly touched on aspects of service with respect to appropriate setting for imaging of TIA patients, the importance of commencing antiplatelet therapy urgently and specialist review, with care organised in a structured pathway. The debate regarding whether TIA patients should be admitted to hospital or managed as outpatients depends on the availability of expertise and organisation of services at the national and local level. For example, in France, large resources have been devoted to the establishment of a centre of excellence providing 24-h outpatient TIA services for all of Paris, staffed by vascular neurologists who also provide neurosonology services. In the Oxford model, general practitioners triage patients to either hospital care or to an express TIA clinic, but it is not clear how they decide on which course to take. While it appears that the Stanford model used the ABCD2 score for triaging (score 0–3 to outpatient, score 4–5 for CT angiography and score 6–7 for admission), in effect, all patients in this system are seen by a neurologist and investigated within 48 h.

The Australian setting is rather different from those in Europe and North America due to geography, the thinly spread population, paucity of stroke specialists, and lack of access to advanced imaging and specialists in rural hospitals. However, there are essential features in TIA care that may need to be adopted universally. The primary need is that of a structured pathway of care that is geared towards the provision of essential rapid investigations (brain imaging, ECG, carotid studies) and treatments (antiplatelets, anticoagulants, carotid endarterectomy), with a secondary follow-up phase for less urgent investigations and treatments. This requires close collaboration with locally available diagnostic services to deliver timely imaging, a systematic method for checking results of urgent investigations and follow up, and excellent communication between stroke specialists, primary care physicians and vascular surgeons. Depending on region, hospital and availability of resources, this can be either achieved in an inpatient or outpatient setting. There are emerging Australian data that inform on the debate of admission versus non-admission of TIA patients. A poorer short-term outcome (<28 days) was observed in TIA patients (defined by International Classification of Diseases code) discharged from emergency departments compared with those admitted within the Sydney South West Area Health Service between 2001 and 2005. The authors speculated that a delay or omission of appropriate investigations or treatment may account for the difference in outcome, which may have resulted from the lack of a structured TIA pathway and...
less intensive treatment approaches during that time period.\textsuperscript{33} On the other hand, in the recently published Monash TIA Treatment and Triaging (M3T) system, approximately 80\% of TIA patients were managed safely as outpatients after essential acute management was rapidly completed or initiated in the emergency department. M3T uses a pathway-driven approach in a structured setting and is driven by stroke neurologists based at a tertiary teaching hospital. Pathways such as M3T may be achievable in other similar tertiary teaching hospitals, but not in smaller or remote hospitals where significant modifications may be required to account for local expertise and resources.

Using cost utility modelling in the US, it has been suggested that admitting TIA may be justifiable in case these patients require thrombolysis.\textsuperscript{34} This was refuted by a later decision analysis study reporting that urgent access clinic is cost-effective when compared with hospitalisation.\textsuperscript{35} In the only study with patient-level data from the US, the frequency of high-level interventions such as thrombolysis occurred with similar frequency (10\%) in admitted patients classified as either low or high risk using the ABCD2 score.

Provision of an outpatient-based TIA pathway will require investment in personnel but may gain savings in hospital bed use. In our centre, only 19\% of TIA patients are managed as inpatients in our structured TIA pathway.\textsuperscript{5} If it is assumed that the median length of stay for TIA patients is 2 days and approximately 160 TIA presentations per year to our centre, a crude estimate of the annual bed saving alone with respect to TIA care would be as high as AUD$320 000 for 100\% admission, $256 000 for 80\% admission, $192, 000 for 60\% admission, $128 000 for 40\% admission and only $64 000 for 20\% admission.\textsuperscript{5} Such estimates of costs does not take into account the cost of providing an outpatient service and staffing. It should be pointed out that during the period 2004–2007 upon which the M3T cohort was derived, the TIA clinic was operating only 2 days a week, urgent cases outside of this time were seen on the other 3 weekdays (5.9\% of the sample) and the clinic was not open on weekends.\textsuperscript{5} Ultimately, it may require a change in health policy to spur the exploration of models of TIA care that emphasise efficiency and provide an alternative to routine hospital admission.

References


A study of venous thrombosis incidence in patients with acute hyperthyroidism

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Key words
venous thrombosis, deep vein thrombosis, pulmonary embolism, hyperthyroidism, cerebral venous thrombosis.

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Received 7 February 2012; accepted 23 June 2012.


Abstract

Background: Hyperthyroidism is not a widely acknowledged risk factor for venous thrombosis (VT), such as deep vein thrombosis, pulmonary embolism and cerebral VT. Several case reports and case-control studies support an association between VT and hyperthyroidism. Prothrombotic changes in the coagulation pathway in thyrotoxic subjects include reversible elevation of factor VIII and von Willebrand factor, and give biological plausibility to the association and possibly causation for VT.

Aim: We sought to determine the incidence of symptomatic VT in acute hyperthyroidism.

Methods: A retrospective review of consecutive outpatients presenting to the endocrinology clinic at our district hospitals from January 2006 to December 2008 with acute hyperthyroidism was carried out. All occurrences of objectively proven symptomatic VT (deep vein thrombosis, pulmonary embolism and cerebral vein thrombosis) in the 6 months following the diagnosis of hyperthyroidism were sought.

Results: Four hundred and twenty-eight patients were identified, of whom most were female (80%) and relatively young (mean age 47 years). Three patients (0.70%; 95% confidence interval 0.14–2.0%) were identified with a confirmed VT within 6 months of the diagnosis of hyperthyroidism.

Conclusions: Although the literature suggests moderate association between VT and acute hyperthyroidism, our data show that the absolute risk is low. Furthermore, our data suggest that hyperthyroidism is usually an additional risk factor but rarely the sole risk factor for VT.

Introduction

Venous thromboembolism (VTE) presenting as deep vein thrombosis (DVT) or pulmonary embolism (PE) in the general population occurs at an estimated incidence of 0.1% per annum. The aetiology of both diseases is multifactorial with common risk factors being surgery, trauma, oral contraceptive pill (OCP) and malignancy. A less common form of venous thrombosis (VT) is cerebral VT (CVT) with an estimated annual incidence of less than 10 cases per million,1 with risk factors not dissimilar to conventional VTE risks such as thrombophilia, OCP use and malignancy, but also including head and neck infections and chronic inflammatory conditions.2

A recent prospective cohort study has shown a relative risk of 2.31 for PE in those with hyperthyroidism.3 Another case-control study demonstrated that odds ratio for VT rose with increasing free T4 level (with VT odds ratio over 2.8 for those with T4 in the top 5% of the normal reference range) suggesting a 'dose–response' lending plausibility to a causative role in VT.4

Plausible mechanisms for a hypercoagulable state in hyperthyroidism include increased levels of coagulation factor VIII and von Willebrand factor,5–7 endothelial dysfunction5,7 and increased platelet adhesion.8,9 Furthermore, these pathophysiological changes are rapidly reversed with successful treatment of the acute HPT.6–8

Given these data, a case could be made for checking thyroid function tests as part of the routine assessment of a patient presenting with VT not dissimilar to screening patients with new onset atrial fibrillation. It could also be
argued that if the absolute risk of VT is significant in thyrotoxic patients then thromboprophylaxis in high-risk situations might be considered. Furthermore, with the majority of thyrotoxicosis occurring in young women of the child-bearing age,10 should treating physicians consider whether oestrogen use (such as OCP) is appropriate in acutely thyrotoxic women? If the VT risk was significant, at the very least, oestrogen therapy might be deferred until the acute HPT has resolved. In order to inform a clinician’s decision-making about appropriate clinical practice in the earlier and other scenarios, we felt it would be important to establish the absolute incidence of VT in the context of recently diagnosed acute symptomatic HPT.

The aim of our study was to document the incidence of acute VT (CVT, DVT or PE) in the first 6 months following the diagnosis of acute and biochemically confirmed thyrotoxicosis within a general endocrinology outpatient population.

Methods

Study design and subjects

A retrospective clinical records review was performed on all patients referred to and seen at endocrinology outpatient clinics at our district hospitals (North Shore Hospital and Waitakere Hospital, Auckland, New Zealand) over a 36-month period from January 2006 to December 2008.

For inclusion in the analysis, patients had to have either a new onset overt HPT or a recurrence of overt HPT, diagnosed after 1 January 2006. Patients were excluded from the study if they were already receiving therapeutic anticoagulation at the time of diagnosis of HPT or had iatrogenic thyrotoxicosis (i.e. levothyroxine overreplacement). New onset overt HPT was defined as thyroid-stimulating hormone of less than 0.10 mIU/L and an elevation of free T4 and/or free T3 above the upper reference range for normal, occurring in a subject with no prior history of HPT. A recurrence was defined as HPT occurring in a subject with prior history of HPT in whom there was a documented period of biochemical euthyroid remission. Once identified, a review of their hospital clinical and radiology records was performed to determine whether they had objectively confirmed VT in the first 6 months following the diagnosis of acute HPT.

Diagnosis of VT

Symptomatic VT included those patients who had objectively confirmed DVT, PE or CVT. Patients were considered to have DVT on the basis of a compression ultrasound examination of the deep veins of the leg showing non-compressibility of a two contiguous venous segments. PE was confirmed on the basis of an intraluminal filling defect seen in a segmental or larger artery on computed tomography pulmonary angiogram or high-probability ventilation perfusion lung scan in the appropriate clinical setting. CVT was diagnosed on the basis of positive computed tomography or magnetic resonance imaging scan of the cerebral veins showing an intraluminal filling defect.

Patients were defined as being VT negative if clinical records review was negative for VT occurrence and with evidence of continued residence in our district health board as evidenced by either inpatient or outpatient attendance at our district hospitals. These clinical records would capture outpatient and inpatient treatment of VT in New Zealand, as during 2006–2008, subsidised low molecular weight heparin therapy could only be dispensed through a hospital pharmacy on the direction of a hospital clinician.

For patients who had relocated out of our district, we routinely attempted to obtain their new contact details to conduct a follow-up telephone call. If, on repeated attempts, they still could not be contacted or new contact details were not available, no further attempts were made. As we could not clearly determine their VT status, a priori, we decided that these subjects would be removed from our final analysis.

The study protocol was reviewed and approved by the Northern X Regional Ethics Committee of New Zealand (NTX/07/122/EXP).

Outcomes

The primary outcome was the incidence of symptomatic and objectively confirmed VT occurring within the first 6 months following the diagnosis of new or recurrent overt HPT.

Statistical analysis

Descriptive statistics were used to express baseline data and the overall incidence of the primary outcome. All confidence intervals (CI) were calculated using the program CIA version 1.1 MJ Gardner & British Medical Journal, London, UK.11

Results

Subject characteristics

We screened 2192 endocrine outpatient records from January 2006 to December 2008 and excluded 1732 patients because of a non-thyroidal illness, thyroid dysfunction not because of overt hyperthyroidism, or
hyperthyroidism diagnosed prior to 1 January 2006. A further 23 were excluded, as they had either new onset hyperthyroidism but on therapeutic warfarin therapy, or the thyrotoxicosis was iatrogenic. Nine subjects who had moved out of our district and were non-contactable were also excluded from the final analysis (Fig. 1).

Four hundred and twenty-eight patients satisfied the inclusion and exclusion criteria, and their baseline characteristics are summarised in Table 1. There was a clear female preponderance comprising 80% of the study population, and the mean age of study subjects was 47 years (standard deviation ± 16). Half of all subjects were of European ethnicity, and approximately two-thirds had Graves’ HPT.

### Primary outcome

Three of 428 study subjects had a VT episode in the first 6 months after the diagnosis of HPT. This gives an absolute incidence of 0.70% (95% CI 0.14–2.0%) in the 6-month period. Table 2 summarises details of three primary outcome cases.

### Discussion

In this population of relatively young outpatients, the absolute incidence of symptomatic VT occurring within 6 months of overt HPT onset was 0.7% (95% CI 0.14–2.0%). This point estimates appears higher than would be expected from population studies where the background rate of VTE is reported as 0.1–0.14%. In parallel other cohort and case-control studies that had uniformly demonstrated an association of VT and HPT.

Two of the three primary outcome cases had other VT risk factors, namely OCP usage and malignancy. They are not infrequently seen risk factors in general population with or without VT and reflect the multifactorial nature of VT. It illustrates that although HPT by itself may rarely cause VT, it should be taken into consideration when other VT risk factors are present.

Our study has a number of limitations. We attempted to detect a condition (VT) with a relatively low incidence from a moderate sample size, therefore limiting the

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Table 1: Population characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean ± standard deviation)</td>
<td>47.2 ± 16</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>87:341</td>
</tr>
<tr>
<td>Ethnicity (no. (%))</td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>187 (43.7)</td>
</tr>
<tr>
<td>Other European</td>
<td>28 (6.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>108 (25.2)</td>
</tr>
<tr>
<td>Maori and Pacific</td>
<td>53 (12.4)</td>
</tr>
<tr>
<td>Other</td>
<td>36 (8.4)</td>
</tr>
<tr>
<td>Not stated</td>
<td>16 (3.8)</td>
</tr>
<tr>
<td>Cause of hyperthyroidism (no. (%))</td>
<td></td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>282 (65.9)</td>
</tr>
<tr>
<td>Toxic adenoma/multinodular goitre</td>
<td>79 (18.4)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>23 (5.4)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (6.8)</td>
</tr>
<tr>
<td>Not stated</td>
<td>15 (3.5)</td>
</tr>
</tbody>
</table>

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Figure 1: Subject selection.
References


11 Gardner MJ, Altman DG. Statistics with Confidence: Confidence Intervals and
Out of sight, out of mind: an audit of inferior vena cava filter insertion and clinical follow up in an Australian institution and literature review

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Introduction
Percutaneous insertion of inferior vena cava (IVC) filters was developed in 1967¹ and is mainly indicated as a treatment to prevent recurrent venous thromboembolism (VTE) in patients who have contraindications to or failure of anticoagulation in the setting of an acute pulmonary embolism (PE) and/or a deep vein thrombosis (DVT).²,³ However, the lack of randomised controlled trials and well-designed studies looking at the efficacy and safety of IVC filters means that established indications for filter placement are based largely on expert opinion.¹,²,⁴

Key words
IVC, filter, thromboembolism, retrieval, follow up.

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Received 16 March 2012; accepted 23 June 2012.

Abstract
Background: Inferior vena cava (IVC) filters are increasingly used to treat venous thromboembolism when there are contraindications or failure to respond to anticoagulant therapy. Retrievable filters were introduced to avoid long-term complications and risks associated with permanent filters. However, failure to follow up patients appropriately can lead to low retrieval rates.
Aims: To examine the practice of our institution in using retrievable IVC filters and to provide a review of published literature.
Methods: Retrospective audit of medical records in a single medical institution.
Results: Forty-one patients had retrievable IVC filters inserted. The median age of patients was 67. The majority (78%) of patients had filters inserted for presence of venous thromboembolism and contraindication to anticoagulation. Twenty-five (61%) patients received no clinical follow up. Factors associated with loss to follow up include a lack of documentation for retrieval plan (P < 0.01), lack of haematology outpatient clinic review (P < 0.01) and age greater than 50 years (P < 0.01). Procedural success was achieved in nine of 11 attempted filter removals. Eighteen complications were noted among patients. IVC filter insertion failed to prevent recurrent pulmonary embolisms in three patients.
Conclusions: Majority of retrievable IVC filters will become lost to clinical follow up. Rates of attempted retrieval within 1 year of filter insertion are low. Loss to follow up is associated with older age, lack of documentation and lack of haematology clinic review post discharge. This study highlights the importance of a structured system to document clearly the review and retrieval plans for patients with IVC filters, at the time of initial insertion.
help avoid the significant long-term complications associated with permanent filters such as thrombotic occlusion of the IVC, vena cava perforation and migration and embolisation of the filter.2,5–6 Despite the increasing use of retrievable filters, the rates of follow up and retrieval of these filters remain poor.7–9 We conducted a review of the use of retrievable IVC filters in our institution and compared it with published reports in the literature to audit and improve our clinical practice. Our results show that very few patients have documented plans for reviewing and retrieving the IVC filter at the time of hospital discharge, and that the vast majority of retrievable IVC filters are never removed within a year of insertion.

Methods

We identified all hospitalised patients who had retrievable IVC filters inserted by the department of interventional radiology at St Vincent’s Hospital (Melbourne) between July 2007 and December 2009. Patients were identified by searching the radiology database (picture archiving and communication system (PACS)). All medical and radiology records and notes were reviewed from the time of the admission up to 1 year from the date of filter insertion or until the date of filter removal. Data collected included patient demographics, clinical co-morbidities, indications for filter insertion, filter type, clinical units involved, documentation of plans for filter removal, rates of complications and use of anticoagulation at discharge. Patients with DVT had the diagnosis confirmed with ultrasonography, and those with PE had confirmation by ventilation/perfusion lung scan or computed tomography pulmonary angiography. We reviewed available clinic and re-admission notes to study the rates of follow up of the filters, defined as a clinic appointment to plan for filter removal or hospital admission for filter removal made within 3 months of discharge. Data on complications during filter retrieval were collected. Statistical analysis was performed to compare between categorical variables with the Fischer’s exact test using the statistical software Graphpad (http://www.graphpad.com; GraphPad Software Inc., San Diego, CA, USA), and a P-value of ≤0.05 was considered statistically significant.

Results

Patient characteristics

There were 52 patients who had retrievable IVC filters inserted between the period of July 2007 and December 2009. Six patients had Cook Gunther Tulip Vena Cava Filters (William Cook Europe, Bjaeverskov, Denmark) inserted. The remaining 46 patients received Cook Celect Vena Cava Filters (William Cook Europe).

Of the 11 patients who were excluded from the study, three had no records available, two patients died within 1 month of filter insertion and six patients had filters declared for permanent dwell. Table 1 outlines the characteristics of the 41 patients in the study. Thirty-four (82.9%) patients were aged 50 and above, and the median duration of hospital stay was 21 (range 1–127) days. Almost equal numbers of filters were ordered by surgical (N = 18) and medical units (N = 19).

Most (78%) patients had IVC filter insertion for transient contraindications to anticoagulation in the setting of a confirmed diagnosis of VTE. Table 2 outlines the indications for IVC filter insertion. In the absence of institutional guidelines at the time of the study, the decision for IVC filter insertion was made by the treating team, with or without consultations with other teams.
Follow up of IVC filters

Among the 41 patients who received an IVC filter, only 16 (39%) patients received follow up in the form of clinic appointments made to plan for filter removal, or re-admissions to hospital for filter removal within a period of 3 months from discharge. Table 3 summarises the different characteristics and factors associated with the follow up of patients with IVC filter insertion. Patient factors that were found to be significantly associated with loss to follow up included age \( \geq 50 \) (\( P < 0.01 \)), lack of haematology outpatient clinic follow up (\( P < 0.01 \)) and lack of documentation of a plan for filter removal during admission (\( P < 0.01 \)).

Of the 32 patients who had filters because of VTE and transient contraindication to anticoagulation, 17 (53.1\%) were lost to follow up (Table 4). Five of six patients with prophylactic insertion of filters were lost to follow up. It was also noted that at discharge, 29 patients were on therapeutic anticoagulation, and 24 patients had documented plans for the duration of anticoagulation.

Retrieval of filters

Eleven of 41 (26.8\%) patients had attempted retrieval within a year of insertion (Table 5). Among the 30 patients who had no attempted retrieval, only six patients had documented reasons of contraindications to filter removal. One patient who had attempted retrieval performed was initially lost to follow up and had to be re-referred back to the hospital for retrieval of the filter on request of the patient.

Our centre managed to retrieve nine filters successfully. Four of these had a dwell of between 42 days and 90 days, while four filters had a dwell of between 91 days and 236 days. Of the two patients who had unsuccessful retrieval, one was an 18-year-old patient who was noted to have significant intra filter thrombosis and perforation of filter through the wall of the IVC preventing retrieval after a dwell of 64 days. The other patient was 61 years old who had been lost to follow up and was referred back for filter removal after a dwell of 236 days. Failure of removal was due to IVC filter endothelisation and migration of the filter leg through the IVC wall.

Post-insertion complications

Complications were only noted at time of retrieval or if investigations were performed for clinical symptoms or suspicion. Two patients had immediate complications following filter insertion (tilting of the filters). Other complications observed are summarised in Table 6. The most common complication documented was recurrent VTE. Six patients died during their duration of follow up, all from causes attributed to other medical conditions not related to the filter.

Discussion and review of literature

There is still uncertainty surrounding the efficacy and safety of IVC filters due to lack of good randomised controlled studies. Expert committees recommend that retrievable filters be used if the patient has a temporary contraindication to anticoagulant therapy and that all patients with IVC filters should receive clinical follow up to assess for filter associated complications, appropriateness of continual anticoagulation and appropriate retrieval of the filter. Seshadri et al. found that only 20 of 42 Gunther tulip filters inserted were planned for removal.
Of the 22 filters left in situ, six filters lacked any documented contraindications to removal. Mission et al. noted that 167 of 240 (69.6%) patients who had retrievable IVC filter insertion had no documentation for filter retrieval and that 36 (21.6%) of these patients had no contraindication to filter retrieval. In our study, although it could be argued that it was reasonable for the three patients who had IVC filters insertion for breakthrough VTE to have permanent filters, there was still failure to document a decision regarding this.

Younger patients (<50 years of age) were more likely to be followed up possibly due to heightened concerns regarding the long-term complications of filters. Better follow-up rates among younger patients were also noted in other studies. Follow up was comparatively poorer (70.6% compared with 14.3%) in the older patients.

Table 3 Characteristics of patients who had IVC filter insertion

<table>
<thead>
<tr>
<th>—</th>
<th>Patients with follow up</th>
<th>Patients lost to follow up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 16</td>
<td>n = 25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n (%) or mean ± SD</td>
<td>n (%) mean ± SD</td>
<td></td>
</tr>
</tbody>
</table>

**Age (years)**

- <50: 6 (85.7%) 1 (14.3%) <0.01
- ≥50: 10 (29.4%) 24 (70.6%)

**Gender**

- Female: 8 (50%) 8 (50%) 0.33
- Male: 8 (32%) 17 (68%)

**Co-morbidities**

- Chronic heart/lung disease: 7 (50%) 7 (50%) 0.33
- CNS haemorrhage: 2 (25%) 6 (75%) 0.45
- Neurosurgical procedure: 3 (50%) 3 (50%) 0.66
- Malignancy: 6 (35.3%) 11 (64.7%) 0.75
- Previous VTE: 5 (41.7%) 7 (58.3%) 1.00

**Patients planned for further interventions/operation**

- 4 (66.7%) 2 (33.3%) 0.19

**Patient’s place of residence**

- Patients residing in regional Victoria§: 6 (42.9%) 8 (57.1%) 0.75
- Metropolitan patients: 10 (37.0%) 17 (63.0%)

**Discharge destination**

- Transfer to another hospital on discharge: 3 (21.4%) 11 (78.6%) 0.18
- Discharged home: 13 (48.1%) 14 (51.9%)

**Duration of hospital stay (mean ± SD) (days)**

- 37.6 ± 28.6 23.9 ± 30.3

**Anticoagulation**

- Documented plan for anticoagulation‡ at discharge: 12 (50%) 12 (50%) 0.11
- No documented plan for anticoagulation‡ at discharge: 4 (23.5%) 13 (69.3%)
- Therapeutic anticoagulation‡ at discharge: 12 (41.4%) 17 (58.6%) 0.73
- No therapeutic anticoagulation‡ at discharge: 4 (33.3%) 8 (66.7%)

**Units ordering filters**

- Surgical units: 6 (33.3%) 12 (66.7%) 0.54
- Medical units: 10 (52.6%) 9 (47.4%) 0.12
- External units: 0 (0%) 4 (100%) 0.14

**Documentation of plan for IVC filter removal**

- Documented plan: 12 (63.2%) 7 (36.8%) <0.01
- No documented plan: 4 (18.2%) 18 (81.8%)

**Discussion with haematology**

- Inpatient haematology consults: 5 (50%) 5 (50%) 0.47
- No inpatient haematology consults: 11 (35.3%) 20† (64.7%)
- Haematology outpatient follow up: 7 (87.5%) 1 (12.5%) <0.01
- No haematology outpatient follow up: 9 (27.3%) 24 (72.7%)

†One patient was under the haematology unit. ‡Therapeutic anticoagulation with low molecular weight heparin, warfarin or intravenous heparin.

§Patients from regional Victoria were patients residing in an area classified as RA2 to RA5 in accordance with the Australian Standard Geographical Class Remoteness Area classification system. The classification system is as follows: RA1, major cities of Australia; RA2, inner regional Australia; RA3, outer regional Australia; RA4, remote Australia and RA5, very remote Australia. The categories are defined in terms of remoteness – which is calculated using the road distance to the nearest urban centre in each of the five classes based on population size. *, **, ***Significant P-values. IVC, inferior vena cava; SD, standard deviation; VTE, venous thrombotic event.
(aged ≥ 50), who comprised the majority (82.9%) of the study cohort. Patients who were booked in for haematology outpatient clinic post-insertion of filters tended to have better rates of follow up perhaps because of heightened clinician awareness of filter associated complications that encouraged them to be more proactive in advocating for filter removal. Documentation of a removal plan at discharge or during the initial admission was also important in ensuring follow up of patients with IVC filters. Twenty-two of 42 (53.7%) patients did not have a documented plan for retrieval during the initial admission, and 18 of these patients subsequently became lost to hospital follow up.

Table 4 Indications for filter insertion versus rates of follow up

<table>
<thead>
<tr>
<th>Indications</th>
<th>Followed up</th>
<th>Lost to follow up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE and transient contraindication to anticoagulation</td>
<td>15 (46.9%)</td>
<td>17 (53.1%)</td>
<td>0.07†</td>
</tr>
<tr>
<td>Breakthrough VTE while on therapeutic anticoagulation</td>
<td>9 (33.3%)</td>
<td>16 (66.7%)</td>
<td>0.27‡</td>
</tr>
<tr>
<td>Prophylactic insertion/VTE and no contraindication to anticoagulation</td>
<td>1 (16.7%)</td>
<td>5 (83.3%)</td>
<td>0.38§</td>
</tr>
</tbody>
</table>

†P = 0.07 was derived from comparing follow up of patients with VTE and contraindications to anticoagulation versus patients who received filters for other reasons (i.e. patients with breakthrough VTE while on therapeutic anticoagulation and patients who had prophylactic insertion/VTE and no contraindication to anticoagulation. ‡P = 0.27 was derived from comparing follow up in patients who had breakthrough VTE while on therapeutic anticoagulation vs patients who received filters for other reasons (i.e. patients who had VTE and contraindications to anticoagulation and patients who had prophylactic insertion/VTE and no contraindication to anticoagulation). §P = 0.38 was derived from comparing follow up in patients with prophylactic insertion/VTE and patients who received filters for other reasons (i.e. patients who had VTE and contraindications to anticoagulation and patients who had breakthrough VTE while on therapeutic anticoagulation). SD, standard deviation; VTE, venous thrombotic event.

Table 5 Length of dwell of filters among patients who had attempted retrieval

<table>
<thead>
<tr>
<th>Length of dwell of filter (days)</th>
<th>Number of patients (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successfully removed filters</td>
<td>9</td>
</tr>
<tr>
<td>0–30</td>
<td>1</td>
</tr>
<tr>
<td>31–90</td>
<td>4</td>
</tr>
<tr>
<td>91–365</td>
<td>4</td>
</tr>
<tr>
<td>Failure to retrieve</td>
<td></td>
</tr>
<tr>
<td>0–30</td>
<td>0</td>
</tr>
<tr>
<td>31–90</td>
<td>1</td>
</tr>
<tr>
<td>91–365</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 6 Complications associated with IVC filters

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent PE</td>
<td>10</td>
</tr>
<tr>
<td>Recurrent DVT</td>
<td>3</td>
</tr>
<tr>
<td>IVC thrombus</td>
<td>4</td>
</tr>
<tr>
<td>Suspected infection of filter</td>
<td>2</td>
</tr>
<tr>
<td>Migration/angulation of filter</td>
<td>2</td>
</tr>
<tr>
<td>Endothelisation of filter</td>
<td>1</td>
</tr>
<tr>
<td>Erosion/penetration of IVC wall by filter</td>
<td>1</td>
</tr>
<tr>
<td>Tilting of filter at insertion</td>
<td>2</td>
</tr>
</tbody>
</table>

†Recurrent PE or DVT as demonstrated by ventilation/perfusion scan, pulmonary angiography or ultrasound. DVT, deep vein thrombosis; IVC, inferior vena cava; PE, pulmonary embolism; VTE, venous thrombotic event. It has been demonstrated that instituting a data base and a dedicated follow-up programme has been effective in improving retrieval rates.18,19 Kalina et al. demonstrated that keeping a filter registry improved retrieval rates from 15.5% to 31.5% (P < 0.001) among 307 patients.18 Gasparis et al. noted that having patients followed up by a dedicated nurse practitioner resulted in retrieval rates of 70% compared with their baseline rate of 18% (P < 0.001).19

Indications for IVC filter insertion are based mainly on expert opinion as there is a paucity of randomised controlled trials to demonstrate which groups of people truly benefit from filter placement.4,6,10 The most established indications for IVC filters are in patients with VTE and a contraindication to anticoagulation.1–3,6,20 Thirty-two (78%) of 41 patients received IVC filters in accordance with this guideline. The PREPIC study, which was one of the only two randomised control trials included in a recent Cochrane review on IVC filters,10 excluded patients who had a contraindication to anticoagulation.21 Filter insertion is not recommended as a first-line treatment in patients with VTE who have apparent anticoagulation failure. Treating clinicians are instead advised initially to consider increasing the treatment intensity of oral anticoagulant therapy (aiming for an international normalised ratio of 3.5) or switching to therapeutic dose low molecular weight heparin22 prior to choosing filter placement. Three of our patients received filters for
breakthrough VTE. One had sub-therapeutic anticoagulation with heparin when he developed a PE, while the other two patients were receiving therapeutic cloxane when they had a PE and extension of a DVT respectively. Other instances where insertion of IVC filters may be indicated include patients with VTE and the following conditions: limited cardiopulmonary reserve, preoperative patients or pregnancy. More controversial indications of IVC filters include the use for free-floating thrombus, cancer patients, and as primary prophylaxis in major trauma patients or surgical patients at high risk of a DVT. In clinical practice, decisions to insert IVC filters for reasons that are outside the established guidelines are common. Six of our patients had IVC filters inserted outside established guidelines. Three patients had extensive DVT but no contraindication to anticoagulation. Another three patients had a history of PE and no proven acute VTE at the time of admission, but were unable to have anticoagulation continued due to impending surgery or gastrointestinal bleeding.

Filters have been demonstrated effectively to prevent recurrent PE. However, they are also associated with increased incidence of recurrent DVT. Decousus et al. randomised 400 patients with proximal DVT to receive or not receive permanent filters and were administered either enoxaparin or heparin as anticoagulation. The patients were followed up at 12 days, 2 years and 8 years, and rates of recurrent VTE, death and major bleeding were noted. The trial and its follow-up study found that the rates of PE were lower in patients with IVC filters at 12 days (1.1% compared with 4.8%; \( P = 0.03 \)) and 8 years (6.2% compared with 15.1%; \( P = 0.008 \)). The rates of recurrent DVT were noted to be increased in the filter group at 2 years (20.8% compared with 11.6%; \( P = 0.02 \)) and 8 years (35.7% compared with 27.5%; \( P = 0.042 \)), and there was no significant difference in mortality at 12 days, 2 years and 8 years. Although the number of patients in our study was too small to draw conclusions, we found that IVC filters failed to prevent recurrent PE in three (7.3%) of our patients. Four patients developed recurrent DVT. It has been suggested that the increased incidence of DVT in patients with an IVC filter in situ may be due to the thrombotic occlusion of filters leading to venous stasis in the lower limbs.

It is currently recommended that anticoagulation should be considered when temporary contraindication to anticoagulant therapy is no longer present and that duration of anticoagulation should not be dictated solely by the presence of a filter. The current literature comprises of clinical trials with limited duration and heterogeneous intensity of anticoagulation, making it difficult to conclude what the optimal duration of anticoagulation should be in patients with IVC filters. In the absence of trial data, we agree with the current guidelines that patients with IVC filters should receive anticoagulation once contraindications to anticoagulation remit and should continue on anticoagulation for a duration that is appropriately based on the perceived thrombotic risk of the underlying condition unless there are strong contraindications such as co-morbidities or risk of bleeding. We recommend that patients continue being on anticoagulation for as long as the filter remains in situ given the risk of recurrent DVT and filter thrombosis. Twenty-four (58.5%) patients had documentation for the intended duration of anticoagulation, and 29 (70.7%) patients were on therapeutic anticoagulation at the time of discharge. This is comparable with studies done by other institutions.

Immediate and early complications associated with filter insertion include insertion site haematoma, pneumothorax, extravascular penetration or entrapment of guidewire, tilting, angulation, embolisation of filter, insertion site thrombosis and infection. Intra filter thrombosis ranks as the most frequent complication with a rate of 6–30% of all cases. This was seen in one patient, while another two patients developed IVC thrombosis distal to the filter. Immediate complications relating to filter insertion were low with only two cases of filter tilt recorded. IVC perforation and migration were noted in two of our patients and were only discovered during attempted retrieval of the filter, leading to the procedure being abandoned. IVC perforation has been associated with a longer indwelling time. Although it is more than often an asymptomatic complication with no substantial clinical significance, it can on occasion lead to bleeding or perforation of surrounding organs. Migration of the filter is usually minor and clinically inconsequential, with rates in the literature reported as between 3% and 69%. but it can be potentially life threatening if the filter or fragments of the filter embolise and migrate towards the heart. Death directly related to insertion of the IVC filter is a rare event with a rate of 0.12%. None of our patients died at the time of filter insertion. There are no documented differences in the literature comparing the side effect profile between Cook Gunther Tulip filters and Cook Celect filters.

The mean dwell of a retrievable filter can range anywhere from 9–150 days before attempted retrieval with retrieval success rates ranging between 78% and 100%. Some studies done have shown that filters can be successfully removed up after more than 3 months of dwell, while others show that prolonged dwell decreases the rates of successful retrieval. Studies done to find the optimal retrieval time frames are mostly case series or prospective trials using different types of IVC.
filters,27 hence making it difficult to draw any firm conclusions about the optimal retrieval time. It is currently recommended that filters be retrieved once protection from PE is no longer required.12 Our centre was successful in removing 81.8% of the 11 filters that had attempted retrieval. Five of 11 filters had dwells of more than 3 months.

Our retrospective study was limited by its small sample size, short follow-up time and availability of medical records. Patients who had no clinic appointments documented with the hospital may have had follow up with their general practitioners or have been referred to a private physician or another hospital for follow up. Due to the lack of institutional guidelines for radiological or clinical follow up for our patients, we may have underestimated the number of patients with recurrent VTE and complications associated with the filter as these were only detected when symptoms prompted further investigation. However, the findings from this audit serve as valuable information to encourage a review of our hospital’s policies for IVC filter insertion and follow up.

Conclusion

Our study shows that documented follow up of retrievable IVC filters in our institution is not optimal (61%). The lack of documentation of a plan for retrieval during initial admission, clinic follow up and younger age are associated with loss to follow up. Filters that are lost to follow up are rarely retrieved. Most (78%) of our patients have filters inserted for established indications. Filters may not always be efficacious in preventing PE and can be associated with recurrent DVT and IVC thrombosis. If retrieval is attempted, most (81.8%) filters are successfully retrieved within 1 year of insertion.

Recommendations for changes that are currently being reviewed for implementation include

1 Providing written information for the patient and requesting teams regarding the need for filter removal.
2 Mandatory request for haematology consult prior to filter insertion and referral to a clinic for follow up post-filter insertion.
3 Ensuring clinic follow up till removal of filter and assigning a dedicated nurse practitioner to follow up patients.
4 Providing effective communication to general practitioners and primary care physicians of the patient through clear documentation of filter insertion with an emphasis on filter removal if indicated.
5 Promoting effective communication among interventional radiology, haematology and treating teams.

There are plans to conduct a prospective study to see if implementation of changes makes a significant impact on follow up and retrieval rates.

Acknowledgements

The authors thank Dr Efrant Harnaen (Royal Children’s Hospital, Melbourne) for helping with spreadsheet design and suggestions for study design, data manipulation and proofreading.

The authors also thank Mr Kevin Batty and Ms Siva Sathianandhan (St Vincent’s Hospital, Melbourne) for recalling patient folders.

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12 United States Department of Health and Human Services. Removing retrievable inferior vena cava filters: initial


How receptive are patients to medical students in Australian hospitals? A cross-sectional survey of a public and a private hospital

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Keywords
students, medical; hospitals, private; patient participation, cross-sectional studies; questionnaires.

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Received 21 May 2012; accepted 8 July 2012.

Abstract
Background: Medical student numbers in Australian universities have more than doubled since 2000. There are concerns about the ability for existing clinical training sites to accommodate this increase in student numbers, and there have been calls to increase training in private hospitals. The receptiveness of patients in private hospitals will influence the success of such placements.

Aims: We aimed to evaluate whether patients in a private hospital are as receptive to medical students as patients in a public hospital.

Methods: Cross-sectional survey of patients conducted at a private and a public teaching hospital in Melbourne, Australia. Main outcome measures were willingness to allow a medical student to participate in an interview, physical examination and procedures (electrocardiogram, venepuncture and digital rectal examination), and patient attitudes towards medical students as assessed by a series of 20 attitude statements and a summative attitude score.

Results: Patients at the private hospital were more willing than patients at the public hospital to allow a medical student to take their history unsupervised (112/146, 76.7% vs 90/141, 63.8%; \( P = 0.02 \)). The distribution of patient willingness did not otherwise differ between hospitals for physical examination or procedures. There was no difference in the mean attitude score between hospitals (15.3 ± 0.8 private vs 15.4 ± 1.2 public, \( P = 0.38 \)), and responses differed between hospitals for only four of the 20 attitude statements.

Conclusions: Our findings suggest that patients in a private hospital are at least as receptive to medical students as patients in a public hospital.

Introduction
Clinical placements are a vital component of medical student education. These placements provide students with the opportunity to develop their clinical skills, interpersonal skills and sense of professional identity by interacting with patients, doctors and other healthcare staff. These experiences also act as powerful motivators for student learning.1–3 Despite advances in novel educational strategies, such as simulation, clinical placements are still considered a fundamental component of medical student education.4,5

In Australia, a large proportion of clinical placements have traditionally occurred in public hospitals.6 Since 2000, the number of medical students in Australian universities has more than doubled,7 and there is evidence that public hospitals are struggling to accommodate this rapid increase in medical student numbers.8,9 One proposed solution is to increase clinical placements in ‘non-traditional’ settings, such as private hospitals.9,10 The success of such placements is in part dependent on patients in that setting being receptive to contact with medical students. If patients in private hospitals are not receptive towards medical students, then this could compromise the educational benefit of clinical training in this setting.

We sought to compare the receptiveness of patients in a private hospital to patients in a public hospital. In particular, we aimed to answer (i) if patients in a private hospital are as willing as patients in a public hospital to see medical students and (ii) if patients in a private hospital have similar attitudes towards medical students as patients in a public hospital. Our hypothesis was that
patients in a private hospital would be at least as recep-
tive to medical students as patients in a public hospital.

**Methods**

**Study design and setting**

The study was a cross-sectional survey of patients from Cabrini Hospital Malvern (a 500-bed private hospital) and The Alfred (a 350- to 390-bed public hospital) in Melbourne, Australia. Both hospitals provide clinical training for medical students from Monash University. Ethical approval was obtained from the human research ethics committees of Cabrini Health, Alfred Health and Monash University. The study was conducted between June and August 2011.

**Questionnaire**

A self-administered multiple-choice patient question-
naire was developed from examples in the literature. We piloted the questionnaire with 10 patients who were not included in the study, and minor changes to the wording of some questions were made to improve clarity.

The questionnaire consisted of three parts. The first part collected demographical data, including information about the patient’s admission and their previous encounters with medical students. Patients were also asked to rate their current ‘wellness’ on a 10-point scale, where 1 was ‘completely unwell’ and 10 was ‘completely well’.

The second part asked patients if they would be willing to allow a medical student to participate in their history, examination and procedures (electrocardiogram (ECG), venepuncture, digital rectal examination (DRE)). For each clinical task patients were asked to indicate whether they would:

- Allow the student to perform the task with or without supervision
- Allow the student to perform the task, but only with supervision
- Only allow the student to observe the task
- Not allow the student to be present during the task.

No option was listed for a student to perform a DRE without supervision, as this does not occur in practice. Patients were asked to respond to each question as if the request was made to them that day, and they were told to assume that each procedure was required. Patients were provided with written information about each procedure, which described the purpose of the procedure, what it involved and any potential risks.

The third part of the questionnaire assessed patient attitudes towards medical students using a modified version of the ‘Attitudes to Student Doctors Inventory (ASDI)’. Our version consisted of a series of 20 attitude statements about medical students, half of which were worded positively and half negatively. Patients were asked if they agreed or disagreed with each of the statements. An ‘attitude score’ was calculated for each patient by adding the number of positive statements with which they agreed and the number of negative statements with which they disagreed to produce a summative score out of 20. An attitude score was only generated for patients who answered the entire series of 20 attitude statements.

**Participants and recruitment**

We surveyed patients admitted to the general medical unit at each hospital. These units are typically involved in medical student teaching, so the receptiveness of these patients towards medical students is of particular relevance.

Medical students on placement in hospitals are encour-
aged to approach patients on their own in order to practise their clinical and interpersonal skills. This allows students to experience a greater breadth and depth of patient interactions than would be possible if students only saw patients when the staff was available to supervise them. In order to simulate this process, participants in this study were recruited by a medical student (MT). MT recruited participants across both sites using a prepared script.

On each recruitment day, MT obtained a list of all current general medical inpatients at each site. These patients were then assessed for their eligibility to partici-
pate based on them being (i) at least 18 years of age, (ii) able to communicate in English, and (iii) free of any cognitive or physical impairment that would prevent them from completing the questionnaire. These criteria were applied with the assistance of hospital staff who were familiar with the patient and had been familiarised with the questionnaire during an introductory session.

MT then visited all eligible patients to explain the purpose of the study and to invite them to participate by completing a questionnaire. Patients who agreed received a patient information sheet, a questionnaire and an unmarked envelope to return the questionnaire. MT arranged a time to return and collect questionnaires from participants. Consent was assumed from the return of a completed questionnaire.

**Statistical methods and sample size**

The primary outcome was a comparison between hospi-
tals of patient willingness to involve medical students in their care and their attitudes towards students. It was calculated that 118 completed questionnaires from each hospital would be required for the study to have 80% power to detect an absolute difference in proportions of
15% between groups at a 5% significance level. For all categorical variables, comparisons between hospitals were made using Chi-squared tests. For continuous variables (age, self-reported wellness and attitude score), mean and standard deviations were calculated, and t-tests were performed. No adjustment was made to significance level for multiple testing.

Because medical students are encouraged to approach patients on their own, we also dichotomised responses for clinical tasks, other than DRE, into ‘would allow student to perform with or without supervision’ versus other responses. DRE was not included in this analysis as the task cannot be performed by a medical student without supervision. We investigated independent associations between the dichotomised responses and participant characteristics that were different for the two hospital settings using logistic regression. Predictors of attitude score were assessed using multiple linear regression models. Terms were included in models if they were significant at the 5% level.

All significance tests were two-tailed and a P-value of less than 0.05 was considered statistically significant. Data were analysed using Stata/IC 11.2 for Mac (StataCorp, College Station, TX, USA).

**Results**

A total of 360 patients met the inclusion criteria (162 private; 198 public). Figure 1 shows a flowchart for the conduct of the study. The participation rate at the private hospital was significantly higher than at the public hospital (146/162, 90% vs 142/198, 72%; P < 0.01).

**Participant characteristics**

The characteristics of the participants at each hospital are shown in Table 1. There was no difference in sex distribution between hospitals or mean self-reported wellness. Patients at the private hospital were significantly older, more likely to report having completed higher levels of education, to be admitted as a private patient, to have private health insurance and to have a Department of Veteran’s Affairs entitlement card. Patients at the public hospital reported significantly more prior encounters with medical students. Among those with prior encounters, there was no difference in satisfaction between hospitals.

**Patient willingness**

Patient willingness to allow a medical student to be involved in a history, physical exam and procedures is shown in Table 2.

There was a significant difference in the distribution of patient willingness to allow a student to be involved in a medical interview (χ² = 10.14, d.f. = 3, P = 0.02). This was largely due to a higher proportion of patients at the private hospital being willing to allow a student to take their history without supervision (112/146, 76.7% vs 90/141, 63.8%; χ² = 5.71, d.f. = 1, P = 0.02). There were no differences between hospitals in the distribution of patient willingness to allow a student to be involved in a physical examination, ECG, venepuncture or a DRE.

Logistic regression indicated that patients in the public hospital were less willing to allow a medical student to perform, with or without supervision, an interview (odds ratio (OR) = 0.37; 95% confidence interval (CI) 0.24–0.57), an ECG (OR = 0.53; 95% CI 0.34–0.81) or a venepuncture (OR = 0.57; 95% CI 0.36–0.91). There was no difference between hospitals in willingness of participants to allow students to perform an examination with or without supervision. Age, gender, education level, insurance status or having had a previous encounter with medical students did not contribute further to any of these associations.

**Patient attitudes**

Patient responses to the series of attitude statements are presented in Table 3. There were four attitude statements that differed in the proportion of patients who agreed with the statement at each hospital. Patients at the public hospital were significantly more likely to agree with the statements ‘I would be too embarrassed to see a student’ and ‘I am concerned that seeing a medical student would affect my privacy’. Patients at the private hospital were significantly more likely to agree with the statements ‘a student would have more time for the patient than a doctor’ and ‘I think that it is important for students to get lots of hands on experience with real patients’.

There was no difference in the distribution of attitude scores between hospitals (χ² = 7.28, d.f. = 8, P = 0.51) or in the mean attitude score (t = 0.88, P = 0.38). Patients at the private hospital had a mean score of 15.3 ± 0.8, and patients at the public hospital had a mean score of 15.4 ± 1.1. This indicates that the average patient at each hospital chose the favourable option in 15 out of the series of 20 attitude statements. Linear regression indicated that attitude scores decreased on average by 0.04 (95% CI 0.01–0.07) for each year increase in age. Hospital type, insurance status, previous encounters with medical students, educational attainment or gender were not significant predictors of attitude score.
Discussion

We found that patients in a private hospital were at least as willing as patients in a public hospital to allow a student to participate in their history, examination and procedures. When we dichotomised willingness to allow students to perform clinical tasks with or without supervision versus other responses, participants in the private setting showed a greater willingness than those in the public setting. We also found that patients in each setting had similar attitudes towards medical students.

Although our main aim was to investigate differences in patient receptiveness between hospitals, it is notable that patients at both hospitals indicated a high level of willingness to see students. Combining both hospitals, 98% of participants were willing to allow a student at least to observe their interview, and 80% were willing to allow a student at least to observe a DRE. However, it is
important also to consider the proportion of patients who were eligible but declined to participate in this study. Our recruitment procedure was designed to mimic how a medical student may actually approach a patient. Patients who declined to participate in this study may have also declined if the student researcher had approached them for clinical education rather than research purposes. However, given the high levels of willingness among the participants in this study and that only 20% of patients approached declined to participate, a reanalysis of our data to account for non-participants would still conclude that the majority of patients would accept some form of student participation in their care. Further, as there were more non-participants at the public hospital than at the private hospital, a reanalysis would not affect our main finding, that is, that patients at a private hospital were at least as willing to see medical students as patients at a public hospital.

The pattern of responses to the series of 20 attitude statements was remarkably similar between the two hospitals, and there was no difference in the distribution of attitude scores. It was pleasing that patients at both hospitals appeared to have overall positive attitudes towards medical students. However, there were four items in the attitude statement series that did differ between hospitals (Table 3). Although statistically significant, caution is required when interpreting these differences, as no correction for multiple comparisons was made. Further, the overall difference in responses to each of these four statements was minimal, and the clinical significance of

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Private†</th>
<th>Public‡</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD) (years)</td>
<td>n = 146</td>
<td>n = 142</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Mean</td>
<td>72.0 (15.0)</td>
<td>61.2 (16.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>p&lt;0.01*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69 (47)</td>
<td>79 (56)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>77 (53)</td>
<td>63 (44)</td>
<td></td>
</tr>
<tr>
<td>Highest education completed, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Year 11 or below</td>
<td>39 (27)</td>
<td>59 (42)</td>
<td></td>
</tr>
<tr>
<td>Year 12 or equivalent</td>
<td>36 (25)</td>
<td>28 (20)</td>
<td></td>
</tr>
<tr>
<td>Trade or vocational training</td>
<td>18 (12)</td>
<td>28 (20)</td>
<td></td>
</tr>
<tr>
<td>Undergraduate level studies</td>
<td>24 (17)</td>
<td>15 (11)</td>
<td></td>
</tr>
<tr>
<td>Postgraduate level studies</td>
<td>28 (19)</td>
<td>10 (7)</td>
<td></td>
</tr>
<tr>
<td>Private admission, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Yes</td>
<td>143 (100)</td>
<td>28 (20)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0 (0)</td>
<td>113 (80)</td>
<td></td>
</tr>
<tr>
<td>Private health insurance, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Yes</td>
<td>134 (92)</td>
<td>57 (40)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12 (8)</td>
<td>84 (60)</td>
<td></td>
</tr>
<tr>
<td>Department of Veterans Affairs entitlement, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Yes</td>
<td>16 (11)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>125 (89)</td>
<td>139 (98)</td>
<td></td>
</tr>
<tr>
<td>Self-reported wellness</td>
<td>n = 142</td>
<td>n = 142</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean out of 10 (SD)</td>
<td>5.7 (2.1)</td>
<td>6.1 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Previous medical student encounters, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>None</td>
<td>55 (38††)</td>
<td>27 (19)</td>
<td></td>
</tr>
<tr>
<td>Once</td>
<td>26 (18)</td>
<td>19 (13)</td>
<td></td>
</tr>
<tr>
<td>2-5 times</td>
<td>42 (29)</td>
<td>42 (30)</td>
<td></td>
</tr>
<tr>
<td>6 or more times</td>
<td>20 (14)</td>
<td>54 (38)</td>
<td></td>
</tr>
<tr>
<td>Satisfaction with previous medical student encounters, n (%)</td>
<td></td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Very satisfied</td>
<td>37 (42)</td>
<td>44 (39)</td>
<td></td>
</tr>
<tr>
<td>Satisfied</td>
<td>42 (48)</td>
<td>47 (41)</td>
<td></td>
</tr>
<tr>
<td>Neither satisfied nor dissatisfied</td>
<td>8 (9)</td>
<td>22 (19)</td>
<td></td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Very dissatisfied</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at P < 0.05. †Private hospital was Cabrini Hospital Malvern, Melbourne. ‡Public hospital was The Alfred, Melbourne. §Numbers for some categories do not sum to 146 because of missing responses. ¶Numbers for some categories do not sum to 142 because of missing responses. ††Numbers do not total 100% because of rounding. SD, standard deviation.
differences of these proportions is unclear. However, it is interesting to note that for each of these four statements patients from the private hospital were more likely to choose the ‘favourable’ response. This suggests that if anything, patients at a private hospital may have subtly more favourable attitudes towards medical students.

The attitude statement series and attitude score have not been validated previously, but we favoured this method of measuring patient attitudes for several reasons. A major challenge when designing our questionnaire was how to measure meaningfully and compare patient attitudes. As Littlewood et al. describe, ‘attitudes are notoriously hard to quantify, and it is hard to compare without quantifying.’ This situation is made more difficult by the breadth and complexity of patient attitudes that have been explored by the previous literature. For these reasons, we favoured a modified version of the ASDI. Our attitude statement series allowed us to sample a wide variety of attitudes, while the summative attitude score provided a simple but illustrative way of comparing patient attitudes between hospitals.

An inherent limitation of using a questionnaire is that patients do not actually have to commit to a student performing the tasks, and there may be differences in what a patient agrees to in real life. Although our questionnaire was anonymous, some participants may still have had a tendency to choose what they considered to be the ‘correct’ answer (social desirability bias).

The focus of this study was to investigate whether a medical student on placement in a private hospital would have the same opportunities to see patients as his or her colleague in a public hospital. Therefore, we were primarily interested in comparing the overall proportions of patients in each hospital who were receptive to medical students rather than whether admission status or any other demographical variable was a predictor of an individual patient’s receptiveness. There were differences in baseline demographics between our hospital groups, including variables that other studies have found to predict patient receptiveness, such as previous encounters with medical students. We found that patients in the private hospital were at least as willing as patients in the public hospital to allow a student to participate in their care even after adjusting for these differences. Of particular note was that 20% of patients at the public

<table>
<thead>
<tr>
<th>Clinical task</th>
<th>Private†</th>
<th>Public‡</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interview, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Would allow student to perform with or without supervision</td>
<td>112 (77)</td>
<td>90 (64)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Would allow student to perform, but only with supervision</td>
<td>19 (13)</td>
<td>39 (28)</td>
<td></td>
</tr>
<tr>
<td>Would only allow student to observe</td>
<td>13 (9)</td>
<td>9 (6)</td>
<td></td>
</tr>
<tr>
<td>Would not allow student to be present</td>
<td>2 (1)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Examination, n (%)</td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Would allow student to perform with or without supervision</td>
<td>73 (50)</td>
<td>72 (51§)</td>
<td></td>
</tr>
<tr>
<td>Would allow student to perform, but only with supervision</td>
<td>49 (33)</td>
<td>55 (39)</td>
<td></td>
</tr>
<tr>
<td>Would only allow student to observe</td>
<td>17 (12)</td>
<td>9 (6)</td>
<td></td>
</tr>
<tr>
<td>Would not allow student to be present</td>
<td>7 (45)</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Electrocardiogram, n (%)</td>
<td></td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>Would allow student to perform with or without supervision</td>
<td>76 (54)</td>
<td>63 (46§)</td>
<td></td>
</tr>
<tr>
<td>Would allow student to perform, but only with supervision</td>
<td>47 (33)</td>
<td>56 (41)</td>
<td></td>
</tr>
<tr>
<td>Would only allow student to observe</td>
<td>13 (9)</td>
<td>14 (10)</td>
<td></td>
</tr>
<tr>
<td>Would not allow student to be present</td>
<td>5 (4)</td>
<td>3 (2)</td>
<td></td>
</tr>
<tr>
<td>Veneupuncture, n (%)</td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>Would allow student to perform with or without supervision</td>
<td>55 (40)</td>
<td>45 (33§)</td>
<td></td>
</tr>
<tr>
<td>Would allow student to perform, but only with supervision</td>
<td>62 (45)</td>
<td>61 (45)</td>
<td></td>
</tr>
<tr>
<td>Would only allow student to observe</td>
<td>20 (14)</td>
<td>26 (19)</td>
<td></td>
</tr>
<tr>
<td>Would not allow student to be present</td>
<td>2 (1)</td>
<td>5 (4)</td>
<td></td>
</tr>
<tr>
<td>Digital rectal exam¶, n (%)</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Would allow student to perform with supervision</td>
<td>61 (45§)</td>
<td>54 (39)</td>
<td></td>
</tr>
<tr>
<td>Would only allow student to observe</td>
<td>46 (34)</td>
<td>63 (46)</td>
<td></td>
</tr>
<tr>
<td>Would not allow student to be present</td>
<td>30 (22)</td>
<td>21 (15)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at P < 0.05. †Private hospital was Cabrini Hospital Malvern, Melbourne. ‡Public hospital was The Alfred, Melbourne. §Numbers do not total 100% because of rounding. ¶No option was listed for a student to perform a digital rectal examination without supervision, as this does not occur in practice.
hospital indicated that they were admitted as a private patient, but including this as an adjustment factor did not change the result.

We only surveyed general medical patients and patients from two large metropolitan hospitals. While our results are promising, further studies of hospitals from other settings may be required to determine the generalisability of our results. Further research in the groups excluded from this study, such as patients who do not speak English and patients with cognitive impairment, is also warranted. These groups make up a significant proportion of Australia’s hospital population, and as future doctors, medical students must gain hands on experience working with these patient groups. We were unable to include these patients in our study because of ethical and practical constraints. Future studies could address this issue by developing individualised recruiting strategies that reflect how each patient group usually gives consent to participate in medical education.

We found no evidence that patients in a private hospital are less receptive to medical students than patients in a public hospital. Within the limitations of this study, this suggests that concerns that patients in private hospitals are more likely to refuse contact with students may be unfounded. Private hospitals operate on a fee for service basis and must offer a service that warrants a financial contribution from patients. It is understandable that doctors and administrators in private hospitals may be reluctant to participate in any activity that may threaten their ability to provide a service that warrants these contributions. Our study found that patients in a private hospital are not only sympathetic to the need to provide future doctors with patient contact but that these patients are overall very willing and positive participants in medical education.

Table 3  Attitude statement series by hospital

<table>
<thead>
<tr>
<th>Item</th>
<th>Total responses per item (private; public)</th>
<th>Private† Agree, n (%)</th>
<th>Public‡ Agree, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 I would see a medical student because it would help the student.</td>
<td>136; 134</td>
<td>134 (99)</td>
<td>128 (96)</td>
<td>0.15</td>
</tr>
<tr>
<td>2 I would see a medical student because it would help the doctors to teach the students.</td>
<td>137; 133</td>
<td>136 (99)</td>
<td>129 (97)</td>
<td>0.17</td>
</tr>
<tr>
<td>3 I would be too embarrassed to see a student.</td>
<td>137; 132</td>
<td>2 (1)</td>
<td>10 (8)</td>
<td>0.02*</td>
</tr>
<tr>
<td>4 A student would have more time for the patient than a doctor.</td>
<td>131; 129</td>
<td>65 (50)</td>
<td>40 (31)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>5 I am worried that I would not have any choice about whether or not I saw a medical student.</td>
<td>137; 130</td>
<td>29 (21)</td>
<td>26 (20)</td>
<td>0.81</td>
</tr>
<tr>
<td>6 I am worried that a medical student would negatively affect the quality of care I receive.</td>
<td>136; 130</td>
<td>15 (11)</td>
<td>21 (16)</td>
<td>0.22</td>
</tr>
<tr>
<td>7 I would be annoyed if I had to repeat my history or examination for a medical student.</td>
<td>136; 132</td>
<td>26 (19)</td>
<td>37 (28)</td>
<td>0.09</td>
</tr>
<tr>
<td>8 Having medical students around would give me the opportunity to help them to better understand my health condition.</td>
<td>137; 132</td>
<td>127 (93)</td>
<td>118 (89)</td>
<td>0.34</td>
</tr>
<tr>
<td>9 Doctors that teach medical students would have no time for the patient.</td>
<td>136; 131</td>
<td>8 (6)</td>
<td>9 (7)</td>
<td>0.74</td>
</tr>
<tr>
<td>10 I feel that I could talk to a student about issues that I am uncomfortable discussing with my doctor.</td>
<td>134; 132</td>
<td>9 (7)</td>
<td>14 (11)</td>
<td>0.26</td>
</tr>
<tr>
<td>11 I would get to learn more about my health condition by listening to a doctor teach a student.</td>
<td>138; 131</td>
<td>110 (80)</td>
<td>105 (80)</td>
<td>0.93</td>
</tr>
<tr>
<td>12 I think that it is important for students to get lots of hands on experience with real patients.</td>
<td>138; 131</td>
<td>138 (100)</td>
<td>123 (93)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>13 Having students around would make me feel unimportant.</td>
<td>134; 132</td>
<td>3 (2)</td>
<td>4 (3)</td>
<td>0.69</td>
</tr>
<tr>
<td>14 On balance, I would prefer that there are no medical students in this hospital.</td>
<td>137; 132</td>
<td>2 (1)</td>
<td>3 (2)</td>
<td>0.62</td>
</tr>
<tr>
<td>15 I think that students should spend more time in lecture theatres and tutorial rooms than in hospitals.</td>
<td>136; 132</td>
<td>8 (6)</td>
<td>4 (3)</td>
<td>0.26</td>
</tr>
<tr>
<td>16 I am concerned that seeing a medical student would affect my privacy.</td>
<td>136; 132</td>
<td>4 (3)</td>
<td>12 (9)</td>
<td>0.03*</td>
</tr>
<tr>
<td>17 Overall, I am glad that this hospital is involved in teaching medical students.</td>
<td>138; 131</td>
<td>133 (96)</td>
<td>119 (91)</td>
<td>0.06</td>
</tr>
<tr>
<td>18 I would not ask the student any questions because they would not know the answers.</td>
<td>137; 131</td>
<td>18 (13)</td>
<td>20 (15)</td>
<td>0.62</td>
</tr>
<tr>
<td>19 Overall, I think I would benefit from having a student around.</td>
<td>136; 129</td>
<td>106 (78)</td>
<td>94 (73)</td>
<td>0.34</td>
</tr>
<tr>
<td>20 I do not mind if a student is inexperienced because they have to learn some how.</td>
<td>138; 130</td>
<td>131 (95)</td>
<td>121 (93)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Significant at P < 0.05. †Private hospital was Cabrini Hospital Malvern, Melbourne. ‡Public hospital was The Alfred, Melbourne.
Conclusion

Patient receptiveness is only one consideration in the planning of any medical student placement. Other issues, such as the range of patient conditions, teaching resources and infrastructure also need to be considered. However, many of these barriers can be addressed by committed and enthusiastic medical schools, hospital staff and policymakers. We feel that private hospitals can play a significant role in the education of Australia’s future doctors.

Acknowledgements

We thank Adjunct Clinical Associate Professor Laila Rotstein for her assistance with patient recruitment at The Alfred and Ms Anne Spence from Cabrini Health for her contribution to the original project idea.

References

Gastroenterology training in Australia: how much is enough?

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Key words
Gastroenterology training, trainee, survey, higher degree, Fellowship, location of training.

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Received 24 September 2011; accepted 13 February 2012.

doi:10.1111/j.1445-5994.2012.02757.x

Abstract
Background: Advanced training in gastroenterology currently consists of 2 years of core training and 1 elective (non-core) year. We surveyed gastroenterologists 2–7 years following completion of training to determine the strengths and weaknesses of their training.

Methods: All gastroenterologists were invited to participate in an anonymous online survey.

Results: There was a 46% response rate (49/110). Eighty-one per cent were male with most aged 36–45. Respondents felt that the current training programme prepared them well for public practice and endoscopy but less well for private practice, ambulatory care, surgical aspects of gastroenterology and functional gastrointestinal disorders. Most had faced challenges transitioning to consultant practice. The majority (53%) spent more than the standard 3 years to complete training in gastroenterology. The top three subspecialty Fellowships were in endoscopy (45%), inflammatory bowel disease (29%) and hepatology (23%). In their elective year, 42% undertook a predominantly clinical year (registrar-type position in general or subspecialty gastroenterology), 28% engaged in research while 24% trained in another specialty. Seventy-eight per cent were in full-time work, and 36% were supervising trainees. Ninety-eight per cent felt that it was beneficial for trainees to move between hospitals during the core years of their advanced training.

Conclusions: The current Australian gastroenterology training programme is generally adequate in preparing trainees for consultant practice but could be improved by increased emphasis on areas such as private practice, ambulatory gastroenterology and functional gastrointestinal diseases. Exposure to a variety of experiences by training in several different hospitals during core training was universally viewed as being important.

Introduction

Advanced training in gastroenterology in Australia consists of 2 years of core clinical training and an elective year. The reasons for this arrangement are based on historical practice without evaluation as to whether it adequately prepares graduates for the workforce. We surveyed Australian-trained gastroenterologists 2–7 years following attainment of their Fellowship to determine the strengths and weaknesses in their training.

Methods

Other surveys have used an online method to increase response rates, and so we have used a similar methodology. An online questionnaire using Survey Monkey (Portland, OR, USA) was devised and sent to all physicians 2–7 years post admission to The Royal Australasian College of Physicians through the Gastroenterology Specialist Advisory Committee. Two reminder emails were sent to increase response rates.

The questions focused on the location of training and the adequacy of both overall and specific areas of training, including elective and subspecialty training. The survey was piloted on current trainees and gastroenterologists to ensure it was able to be completed within 10 min.

Results

There was a 46% response rate (49/110). Eighty-one per cent of respondents were male, with most aged 36–45. Seventy-eight per cent worked full time, with 39% of...
these working more than 50 h a week. Forty-four per cent of female and 14% of male respondents worked part-time. On average, 46% of respondents’ working time was in private practice and 43% in public practice. Thirty-eight per cent were supervisors or co-supervisors of trainees. Forty-six per cent and 57% of respondents were involved in research and teaching respectively.

Location of training

The location of core training, subspecialty training and current consultant practice is summarised in Table 1. Many respondents partook in subspecialty training overseas, but most of these returned to Australia to practise subsequently.

Adequacy of training

Ninety per cent of respondents stated that their training prepared them at least quite well for their current practice (Fig. 1). Ninety-six per cent felt their current practice was completely or mostly in line with what they expected to be doing when they completed advanced training. Although most (54%) had faced some challenges transitioning to consultant practice, such challenges included a perceived need for further clinical training, the time required to partake in research and difficulties in obtaining procedural positions. Participants mentioned needing more exposure to private practice and to the different patterns of disease encountered in that setting (Fig. 2). Many commented that overseas training yielded opportunities which had not previously been expected. Overall, good mentors were felt to be vital.

The particular gaps identified in training included functional gut disorders, liver transplantation, hepatobiliary, oesophageal and rectal disease. Some felt that areas, such as liver transplantation experience, should be compulsory. Insufficient exposure to private practice, ambulatory care, radiology and advanced endoscopy was also commented on. Specifically, the higher prevalence of functional diseases and benign perianal conditions in private practice as opposed to hospital patients was an issue, and increased exposure to these conditions during training was suggested as being useful.

Duration and location of core training

Fifty-five per cent of respondents spent more than the standard 3 years to train (including higher degrees and Fellowships), with 17% taking more than 6 years. Sixty-five per cent stated there should be more than 2 years of core training.

<table>
<thead>
<tr>
<th>Location of core training</th>
<th>Location of subspecialty training</th>
<th>Location of current practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>New South Wales</td>
<td>50%</td>
<td>23%</td>
</tr>
<tr>
<td>Victoria</td>
<td>27%</td>
<td>13%</td>
</tr>
<tr>
<td>Western Australia</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Queensland</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Australian Capital Territory</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>South Australia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Tasmania</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Outside Australia (overseas)</td>
<td>0%</td>
<td>48%</td>
</tr>
</tbody>
</table>
Almost all the respondents (98%) felt that it would be beneficial for trainees to move between hospitals during the core years of training. Comments regarding the reasons for this included the benefits of a wider experience and being exposed to different clinicians and their particular expertise. Some mentioned the need to design rotations to include time on units with differing subspecialty interests, such as transplant hepatology, inflammatory bowel disease and interventional endoscopy. Of the participants, 78% moved between hospitals during their core year. Twenty-two per cent did not move, but all stated it would have been beneficial to do so. Only one participant stated that moving between hospitals would not be beneficial but did not comment as to the reasons for this view.

Elective and subspecialty Fellowships

The elective year was found to be useful for respondents’ clinical practice, career goals and personal life goals in 91%, 93% and 84% respectively. The subspecialty areas in which Fellowships were undertaken are summarised in Figure 3. In the elective year, 71% undertook a clinical registrar year, with 63% of these in gastroenterology and 37% in general medicine. Sixty-five per cent of respondents undertook a subspecialty Fellowship, with 40% taking more than 2 years to complete these.

Twenty-nine per cent engaged in research. Research was felt to be useful if this was continued long term. Many comments emphasised the value of overseas experience and quality supervision. Thirty-nine per cent attained a higher degree, with 39% of these being doctorates of philosophy. The perceived benefits of a higher degree included skills in interpreting research, networking and the development of niche areas in gastroenterology. Higher degrees were often described as a springboard to an academic career. The disadvantages of a higher degree included financial sacrifices and difficulties in re-entering clinical work after basic research. Many commented on other countries requiring research as a compulsory part of gastroenterology training.

Suggestions to improve training included increased funding of research and exposure to private outpatients. Some raised the issue of monitoring clinical experience with logbooks and the possibility of an exit exam.

Discussion

Gastroenterology training is evolving, with increasing recognition of the need for greater structure and coordination between institutions in selecting trainees and providing optimal training. Previous studies have shown that surveying Fellows is a useful method of assessing the adequacy of a training programme. Previous Australian training surveys have concentrated on hours of work and adequacy of exposure to outpatients and/or specialist procedures (including our own accompanying survey of gastroenterology advanced trainees). However, in this survey, we have attempted to measure the adequacy of the ‘end product’, aiming to use this to guide changes in the structure of gastroenterology advanced training over the next few years.

Our response rate of 49/110 (45%) is comparable with other surveys of medical practitioners. Surveys of specialists have a response rate of 36% to 45%, with some studies showing online surveys of medical practitioners
having a 13% response rate. Of note is that 78% were in full-time work and only 39% were working over 50 h per week. This is comparable with another Australian survey of the medical workforce that showed 45% work over 50 h per week, but this survey included general practitioners and hospital resident staff. Interestingly, in our respondents, 44% and 14% of female and male respondents worked part-time. Also of note is that 46% and 57% of respondents were involved in research and teaching respectively.

Overall, respondents felt that their training prepared them well for consultant practice. However, 54% still had challenges in the transition to independent practice. Specific areas of deficiencies centred on transitioning to private practice, liaising with surgical colleagues and specific topics more common in private ambulatory care than in public hospital inpatients. To overcome this, many enrolled in higher degrees or engaged in further clinical training in their elective year. Many elected to increase the duration of their training, with 55% taking more than 3 years to complete specialty training and 17% taking 6 years or more. Forty per cent of participants also undertook a Fellowship of 2 years or more duration.

Qualitative data from comments provided by respondents also provide an insight into how respondents overcame the difficulties. Many utilised mentors and voiced the benefits of partaking in locum jobs to increase their clinical experience in a semi-supervised way. This was particularly useful in transitioning to private practice and is also reflected in the American literature. In particular, working in a large variety of practices prior to setting up their own practice aided many respondents by allowing them to choose a practice model which suited them. Overseas training was highly recommended, and further training was considered essential in areas, such as interventional endoscopy. Financial sacrifices with attaining higher degrees were often mentioned, and increased funding was suggested as a method to improve this. Those who had entered basic research careers expressed similar views.

Our survey revealed an overwhelming view that it was valuable for trainees to move between hospitals during training. The increased breadth of experience and learning was often commented on as the reason for this. Moving between practice settings, including some time in large central city hospitals, suburban hospitals, regional hospitals and private practice will afford trainees a broad view of gastroenterology and expose them to different methods of managing problems. There are clear challenges in implementing such changes, but ultimately, the community, hospitals, patients and the trainees themselves are likely to benefit.

The current duration of training was considered to be too short by many trainees, with at least another year of core training recommended by 65% as being likely to be beneficial. This reinforces similar views in our other study on current gastroenterology trainees who also generally felt that core training should be more than 2 years and also by American and Dutch studies of gastroenterology training. This perception is the likely explanation for 71% of respondents partaking in a clinical year during their elective. Reasons for this may include limited exposure to a range of patients and practice settings, and perhaps an excessive focus on endoscopy by some trainees, leading to inadequate time for other learning activities. While a third clinical year is likely to remain a

Figure 3 Subspecialty Fellowships undertaken.
popular choice for trainees, many will, with personal application and appropriate guidance, manage to cover the core requirements for gastroenterology over 2 years, leaving a ‘true’ elective year for subspecialisation or research.

**Conclusions**

The current Australian gastroenterology training programme is generally adequate in preparing trainees for consultant practice, especially in public hospital work, routine endoscopy and viral hepatology. However, the current programme could be improved by increased emphasis on areas, such as transitioning to private practice, ambulatory gastroenterology, research and functional gastrointestinal diseases. Core training may need to be more than 2 years, and the majority used the elective year for further clinical training. Many engaged in research and attained a higher degree. Finally, exposure to a variety of experiences by training in several different hospitals during core training was universally viewed as being important.

**Acknowledgements**

Thank you to all those who completed the survey.

**References**


Variability in disease burden and management of rheumatic fever and rheumatic heart disease in two regions of tropical Australia


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Key words
acute rheumatic fever, rheumatic heart disease, Aboriginal, Australian, prophylaxis, healthcare quality assurance.

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Received 6 February 2012; accepted 20 May 2012.
doi:10.1111/j.1445-5994.2012.02838.x

Abstract
Background: Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) contribute to Aboriginal Australian and Torres Strait Islander health disadvantage. At the time of this study, specialist ARF/RHD care in the Kimberley region of Western Australia was delivered by a broad range of providers. In contrast, in Far North Queensland (FNQ), a single-provider model was used as part of a coordinated RHD control programme.

Aims: To review ARF/RHD management in the Kimberley and FNQ to ascertain whether differing models of service delivery are associated with different disease burden and patient care.

Methods: An audit of ARF/RHD management. Classification and clinical management data were abstracted from health records, specialist letters, echocardiograms and regional registers using a standardised data collection tool.

Results: Four hundred and seven patients were identified, with 99% being Aboriginal and/or Torres Strait Islanders. ARF without RHD was seen in 0.4% of Aboriginal and/or Torres Strait Islander residents and RHD in 1.1%. The prevalence of RHD was similar in both regions but with more severe disease in the Kimberley. More FNQ RHD patients had specialist review within recommended time frames (67% vs 45%, \( \chi^2, P < 0.001 \)). Of patients recommended benzathine penicillin secondary prophylaxis, 17.7% received \( \geq 80\% \) of scheduled doses in the preceding 12 months. Prescription and delivery of secondary prophylaxis was greater in FNQ.

Conclusions: FNQ’s single-provider model of specialist care and centralised RHD control programme were associated with improved patient care and may partly account for the fewer cases of severe disease and reduced surgical procedures and other interventions observed in this region.

Introduction

Acute rheumatic fever (ARF) is a non-suppurative complication of infection with group A streptococcus (GAS). Its major chronic sequela is chronic heart valve damage associated with rheumatic heart disease (RHD). Rates of ARF and RHD in Aboriginal Australians and Torres Strait Islander peoples are among the highest documented in the world, but these conditions are very rare in non-indigenous Australians. Across the north of Australia, the prevalence of RHD in the Aboriginal and Torres Strait Islander population has been reported at 1–2%. The development of national Australian guidelines for ARF and RHD diagnosis and management has facilitated the standardisation of ARF/RHD care between Australian state health departments. They have been used to inform local management guidelines. Management of ARF and RHD encompasses secondary antibiotic prophylaxis in the form of 3–4 weekly long-acting benzathine penicillin (BP) injections to prevent GAS infection and recurrent ARF, regular local primary healthcare review, echocardiography, specialist review and education.
Management of RHD also involves preventing and managing complications, such as endocarditis, cardioembolism and heart failure, and assessing the need for valve-related surgical procedures.7

Previous studies of ARF/RHD in the north of Australia have demonstrated suboptimal care: secondary prophylaxis coverage is inadequate, survival following heart valve surgery is low and monitoring of anticoagulation is variable.11–13 This earlier work, and the demonstrated high burden of disease, has provided a focus for local initiatives which aim to improve access to, and quality of, care.

The processes and models of local service delivery for comprehensive ARF/RHD care remain variable. This is in part due to historic models of service delivery, geography, and population and health workforce distribution. The Kimberley region of Western Australia (WA) and Cape York and Torres Strait regions of Far North Queensland (FNQ) (Fig. 1) illustrate such variability, with significantly different models of service delivery.

At the time of this review, ARF/RHD care in the Kimberley was based on a ‘multi-provider model’ centred on primary healthcare with support and follow up provided by community-based and outreach specialist service providers. These services included local regional physicians and paediatricians who visited large and small communities, and visiting cardiologists (paediatric and adult) and echocardiographers in larger centres. This involved public and private service providers from a number of different organisations with any required surgery being undertaken in one of three Perth hospitals. Individual primary healthcare sites maintained a variety of paper-based and electronic registers and recall systems with no single regional system.

In FNQ, ARF/RHD care was similarly centred on primary healthcare but with support and follow up provided by a ‘multi-skilled single-provider model’. This consisted of a single specialist outreach service of physicians (who also performed echocardiography) and paediatricians, with adult or paediatric cardiology review generally only provided when surgery was planned at regional referral centres (Cairns or Townsville). Registration and recall of ARF/RHD patients were provided from a regional database supported and coordinated by a centralised ARF/RHD programme.

In order to explore optimal models of care for people with ARF/RHD living in the north of Australia, we undertook an assessment of these two differing systems. This included an assessment of the locally recognised burden of disease, an audit of the care received by patients and benchmarking care against local management guidelines. This process focused on the performance and coordination of care across each region rather than on individual providers.

![Figure 1](image.png) Study sites in the Kimberley (Western Australia) and Far North Queensland.
Methods

We reviewed the management of ARF/RHD patients who had accessed primary and specialist healthcare services in the Kimberley region of northern WA and in the Cape York and Torres Strait regions of FNQ (Fig. 1). In the Kimberley, these services were provided by Aboriginal community-controlled health services and/or state health department primary healthcare clinics and hospitals. In FNQ, they were predominantly provided by health department primary healthcare clinics and hospitals.

Inclusion criteria were a clinician-recorded diagnosis of either: (i) ARF and/or (ii) RHD in patients considered by the local health service to be ‘regular’ clients. A diagnosis of ARF required health record documentation of ARF (irrespective of time of diagnosis and whether ARF was actively managed at the time of audit) or the use of an ARF care plan and, where available, no evidence of RHD on the most recent echocardiogram report. A diagnosis of RHD required documentation of RHD by the local health service with an associated abnormal echocardiogram, or a history of prosthetic valve replacement/valve repair/valvuoplasty, or an echocardiogram report consistent with RHD. Consistent echocardiography findings included: mitral stenosis, mitral regurgitation with thickening and/or distortion of the valve leaflets, or mitral valve and aortic valve regurgitation or stenosis.

Eligible patients were identified at local health services through interrogation of health information management systems (i.e. searching for clients assigned to an ARF/RHD ‘care plan’ or generating ARF/RHD ‘problem’ lists), accessing BP recall lists, and through questioning of local health service staff. In FNQ, the regional ARF/RHD register was also accessed to identify potential clients for inclusion. Finally, electronic copies of specialist letters and echocardiography reports were searched for terms that may indicate the client had ARF/RHD (e.g. rheumatic, mitral, aortic, valve, regurgitation, stenosis), and the health records of clients identified through these methods were checked for diagnoses.

Data were collected in the Kimberley between August and November 2007 at 17 primary healthcare sites and in FNQ between November 2008 and March 2009 at 12 sites (Fig. 1). Data on clinical management were abstracted from local health records (paper-based and electronic), specialist letters, echocardiogram reports and local and regional registers and recall databases. A standardised data collection tool was utilised with a manual providing standardised definitions for patient selection and service delivery.

Data collected and quality measures assessed included: patient demographics; echocardiogram timeliness and results; severity of ARF/RHD based on the classification system proposed by the national guidelines (Table 1); prescription and uptake of secondary prophylaxis in the 12 months prior to audit; timeliness of specialist review (cardiologist, physician, paediatrician); uptake of immunisations (influenza vaccination within past 12 months, pneumococcal vaccination within last 5 years) and appropriateness of anticoagulation. The delivery of health services was benchmarked against local standards of care as outlined in the Kimberley chronic disease protocols and Queensland chronic disease guidelines (Table 2). For those clients receiving secondary prophylaxis, the proportion achieving ≥80% of scheduled doses in the 12 months prior to audit was calculated and any episodes of recurrent ARF for that period were recorded.

Population denominators were based on the 2006 Australian Bureau of Statistics census data. Disease prevalence in the Kimberley was based on the entire Aboriginal and Torres Strait Islander population of the

<table>
<thead>
<tr>
<th>Priority</th>
<th>KIMB</th>
<th>QLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist review</td>
<td>2 years</td>
<td>2 years</td>
</tr>
<tr>
<td>Echocardiography review</td>
<td>2 years</td>
<td>1 year</td>
</tr>
<tr>
<td>Dental review</td>
<td>2 years</td>
<td>1 year</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Priority</th>
<th>KIMB</th>
<th>QLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specialist review</td>
<td>1 year</td>
<td>6 months</td>
</tr>
<tr>
<td>Echocardiography review</td>
<td>1 year</td>
<td>1 year</td>
</tr>
<tr>
<td>Dental review</td>
<td>1 year</td>
<td>1 year</td>
</tr>
</tbody>
</table>

Table 1 Protocol-based classification of severity of acute rheumatic fever (ARF) and rheumatic heart disease (RHD)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>ARF with no evidence of RHD, or trivial to mild valvular disease.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Any moderate valve lesion in the absence of symptoms and with normal left ventricular function; or mechanical prosthetic valves.</td>
</tr>
<tr>
<td>Severe</td>
<td>Severe valvular disease; or moderate to severe valvular lesions with symptoms – shortness of breath, tiredness, oedema, angina or syncope; or tissue prosthetic valves and valve repairs.</td>
</tr>
</tbody>
</table>

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region as clients from all possible healthcare sites were included. Disease prevalence in FNQ was based on population statistics for Local Government Areas associated with those sites audited. Data from Thursday Island were excluded, as accurate population denominator data were not available.

Data were analysed using SPSS (v15.0 for Windows, SPSS Inc., Chicago, IL, USA) and Intercooled Stata 12 (Stata Corporation, College Station, TX, USA). All statistical tests were two sided with a \( P \)-value < 0.05 taken to indicate statistical significance.

This project was approved as a clinical audit by the Western Australian Aboriginal Health Information and Ethics Committee, the Western Australia Country Health Service Board Research Ethics Committee and the Human Research Ethics Committee of the Cairns and Hinterland Health Service District, Queensland Health.

### Results

Four hundred and seven patients were included in the study. Patient demographics, disease prevalence and severity, and valve surgery/procedures are presented in Table 3. There were no significant differences in the demographics of Kimberley and FNQ patients. The prevalence of a previous diagnosis of ARF (with no progression to RHD) and RHD was similar in the two study areas but with more severe disease in the Kimberley. Significantly more RHD patients in the Kimberley had undergone valve surgery or associated procedures.

A history of ARF without associated RHD was seen in 24.5% (52/212) of Kimberley patients and 27.7% (54/195) of FNQ patients. Median age was 22.4 years (inter-quartile range (IQR) 17.2–32.4), and women were overrepresented, accounting for 60.2% of patients. There was no significant difference in age or gender between Kimberley and FNQ ARF patients.

In people with a history of ARF, it is recommended that an echocardiogram be performed at the time of diagnosis (to assess for carditis and pre-existent RHD) and prior to ceasing prophylaxis. FNQ ARF patients were more likely to have had any echocardiogram performed, with 96% (52/54) having a record of an echocardiogram compared with 85% (44/52) of Kimberley patients (\( \chi^2 \), \( P < 0.05 \)).

Evidence of RHD was seen in 75.5% (160/212) of Kimberley and 72.3% (141/195) of FNQ participants. Median age was 30 years (IQR 20 to 43), and women were again overrepresented, accounting for 71.8% of patients.

Overall, 55.1% (166/301) of RHD patients had had a specialist review by a paediatrician, physician or cardiologist in concordance with time frames recommended in local management guidelines. Timely specialist review was more likely for FNQ RHD patients (66.7%, 94/141) compared with Kimberley patients (45.0%, 72/160) (\( \chi^2 \), \( P < 0.001 \)).

Echocardiography was delivered to 60.5% (182/301) of RHD patients within recommended time frames with no overall difference between regions. However, RHD patients in the Kimberley who had a history of valve surgery or other procedures were more likely to have received a timely echocardiogram than comparable patients in FNQ (31/44 (70.5%) vs 9/23 (39.1%), \( \chi^2 \), \( P < 0.001 \)).

### Table 3

Demographics, severity of acute rheumatic fever (ARF)/rheumatic heart disease (RHD) (see Table 1) and prevalence and type of valve surgery/procedure in patients included in this study

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 407)</th>
<th>Kimberley (n = 212)</th>
<th>FNQ (n = 195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median [IQR] (years)</td>
<td>29.1 (18.7–40.2)</td>
<td>29.4 (19.2–41.0)</td>
<td>27.4 (18.3–39.5)</td>
</tr>
<tr>
<td>Female, n [%]</td>
<td>280 (68.8)</td>
<td>141 (66.5)</td>
<td>139 (71.3)</td>
</tr>
<tr>
<td>Aboriginal and/or Torres Strait Islander, n [%]</td>
<td>403 (99.0)</td>
<td>211 (99.5)</td>
<td>192 (98.5)</td>
</tr>
<tr>
<td>Disease prevalence in Aboriginal and/or Torres Strait Islander population, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARF (no progression to RHD)</td>
<td>0.36</td>
<td>0.33</td>
<td>0.41</td>
</tr>
<tr>
<td>RHD</td>
<td>1.07</td>
<td>1.02</td>
<td>1.14</td>
</tr>
<tr>
<td>Disease severity, n [%]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARF/mild RHD</td>
<td>237 (58.2)</td>
<td>101 (47.6)</td>
<td>136 (69.7)*</td>
</tr>
<tr>
<td>Moderate RHD</td>
<td>66 (16.2)</td>
<td>38 (17.9)</td>
<td>28 (14.4)</td>
</tr>
<tr>
<td>Severe RHD</td>
<td>104 (25.6)</td>
<td>73 (34.4)</td>
<td>31 (15.9)*</td>
</tr>
<tr>
<td>Valve surgery or procedures, n (% RHD patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any valve surgery/procedure</td>
<td>67 (22.3)</td>
<td>44 (27.5)</td>
<td>23 (16.3)**</td>
</tr>
<tr>
<td>Mechanical valve</td>
<td>36 (12)</td>
<td>24 (15)</td>
<td>12 (8.5)</td>
</tr>
<tr>
<td>Bioprosthetic valve</td>
<td>13 (4.3)</td>
<td>9 (5.6)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Valvuloplasty/repair</td>
<td>18 (6)</td>
<td>11 (6.9)</td>
<td>7 (5.0)</td>
</tr>
</tbody>
</table>

\*\( \chi^2 \), \( P < 0.0001 \); \**\( \chi^2 \), \( P < 0.05 \). FNQ, Far North Queensland; IQR, interquartile range.
The delivery of secondary antibiotic prophylaxis to ARF/RHD patients is outlined in Table 4. The proportion of patients receiving BP prophylaxis was significantly higher in FNQ than in the Kimberley ($\chi^2$, $P < 0.001$) as was the median number of doses given in the 12 months prior to audit (Wilcoxon Mann–Whitney test, $P < 0.0001$). Ten patients in FNQ and two in the Kimberley with a recommendation for BP prophylaxis had an episode of recurrent ARF in the 12 months prior to the study (Fisher’s exact test, $P < 0.05$). All of these cases were preventable, with no patient receiving adequate secondary antibiotic prophylaxis in the 2 months prior to their episode of recurrent ARF.

One in five RHD patients was receiving warfarin anticoagulation (Table 5). Based on a recommended frequency of coagulation (international normalised ratio (INR)) monitoring of 6 weekly,15 36.7% of these had inadequate monitoring. Of all recorded INR results, 65.1% were outside the recommended range.7 No significant differences were observed between FNQ and the Kimberley.

Influenza and pneumococcal vaccinations are recommended for all patients with ARF/RHD. Influenza and pneumococcal vaccinations were more likely to be up-to-date in FNQ patients (influenza 54.4%, pneumococcal 47.7%) compared with Kimberley patients (38.6%, 37.3%) ($\chi^2$, $P < 0.01$ and $P < 0.05$ respectively).

**Discussion**

This study is the first to highlight differences in the nature and burden of ARF/RHD and the quality of care received by ARF/RHD patients in different northern Australian regions.

Results from this study confirm that in northern Australia, ARF/RHD remains almost exclusively a disease of Aboriginal and Torres Strait Islander people with 99% of identified ARF/RHD patients being of Aboriginal and/or Torres Strait Islander ethnicity. The observed prevalence of RHD in Aboriginal and Torres Strait Islander people in the Kimberley (1.02%) and FNQ (1.14%) was comparable with earlier studies of Aboriginal Australian and low-income country populations.2,3,6,16 This is in contrast to the waning burden of disease among other Australians (0.2% in the Top End of the Northern Territory and less

### Table 4 Recommendation for, and delivery of, secondary antibiotic prophylaxis in the 12 months prior to review

<table>
<thead>
<tr>
<th>Recommendation or prescription for BP, n (%)</th>
<th>All patients (n = 407)</th>
<th>Kimberley (n = 212)</th>
<th>FNQ (n = 195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥80% doses BP given, n (% of those recommended BP)</td>
<td>293 (72.0)</td>
<td>136 (64.2)</td>
<td>157* (80.5)</td>
</tr>
<tr>
<td>Number of doses of BP, median (IQR)</td>
<td>6 (2–8)</td>
<td>4 (1.5–8)</td>
<td>7** (4–9)</td>
</tr>
<tr>
<td>Recommendation for oral antibiotics, n (%)</td>
<td>21/407 (5.2)</td>
<td>0 (0)</td>
<td>21/195*** (10.8)</td>
</tr>
</tbody>
</table>

* $\chi^2$, $P < 0.001$; **Wilcoxon Mann–Whitney test, $P < 0.0001$; ***Fisher’s exact test, $P < 0.0001$. BP, benzathine penicillin; FNQ, Far North Queensland; IQR, interquartile range.

### Table 5 Anticoagulation therapy and rheumatic heart disease (RHD) in the Kimberley and FNQ

<table>
<thead>
<tr>
<th>RHD patients on warfarin, n (%)</th>
<th>All (n = 301)</th>
<th>Kimberley (n = 160)</th>
<th>FNQ (n = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary indication for warfarin, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical valve</td>
<td>60/301 (19.9)</td>
<td>24/37 (64.9)</td>
<td>11/23 (47.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>19/60 (31.7)</td>
<td>10/37 (27.0)</td>
<td>9/23 (39.1)</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td>6/60 (10.0)</td>
<td>3/37 (8.1)</td>
<td>3/23 (13.1)</td>
</tr>
<tr>
<td>Target INR, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Documented in medical record?</td>
<td>49/60 (81.7)</td>
<td>29/37 (78.4)</td>
<td>20/23 (87.0)</td>
</tr>
<tr>
<td>Concordant with national guidelines?†</td>
<td>19/49 (38.8)</td>
<td>8/29 (27.6)</td>
<td>11/20 (55.0)</td>
</tr>
<tr>
<td>INR tests in previous 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number, median (IQR)</td>
<td>11 (5–21.5)</td>
<td>15 (5–26)</td>
<td>9 (6.5–12)</td>
</tr>
<tr>
<td>Adequate testing‡, n (%)</td>
<td>38/60 (63.3)</td>
<td>23/37 (62.2)</td>
<td>15/23 (65.2)</td>
</tr>
<tr>
<td>Results above recommended range, n (%)</td>
<td>180/758 (23.7)</td>
<td>129/517 (25.0)</td>
<td>51/241 (21.2)</td>
</tr>
<tr>
<td>Results below recommended range, n (%)</td>
<td>314/758 (41.4)</td>
<td>232/517 (44.9)</td>
<td>82/241 (34.0)</td>
</tr>
</tbody>
</table>

†National guideline INR recommendations:7 atrial fibrillation without mechanical valve replacement 2 to 3; mechanical mitral valve 2.5 to 3.5; mechanical aortic valve 2 to 3. ‡Based on a minimum recommended monitoring interval of 6 weeks.15 FNQ, Far North Queensland; INR, international normalised ratio; IQR, interquartile range.

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than 0.1% in Central Australia)\textsuperscript{6} and most other high-income nations.\textsuperscript{16,17}

The relatively young median age of RHD patients in this study is presumably related to premature mortality of people with RHD in this setting. This is supported by evidence from the Northern Territory, where the mean age at death of Aboriginal people with RHD is 35.7 years compared with 67.3 years in non-Aboriginal RHD patients.\textsuperscript{1}

The predominance of female patients has been noted previously.\textsuperscript{2,6} Whilst the cause of this remains unclear, it has been suggested that a greater exposure to GAS associated with the care of children, enhanced diagnosis accompanying more frequent healthcare utilisation and a gender-related propensity to autoimmune disease may all contribute.\textsuperscript{18}

While the overall prevalence of ARF/RHD was similar in both regions, we demonstrated a greater proportion of severe RHD and higher levels of valve-related procedures in the Kimberley. This difference may be explained by regional differences in the pattern of ARF/RHD, differences in diagnosis and monitoring, and uptake of secondary antibiotic prophylaxis.

ARF/RHD is associated with economic and environmental disadvantage\textsuperscript{19,20} and incidence of infection with GAS.\textsuperscript{21} However, the available data do not suggest differences in housing, employment, degree of remoteness or income between the Kimberley and FNQ\textsuperscript{22} and there is no obvious reason to suspect that the natural history of ARF/RHD differs between the two regions.

It is possible that cases of ARF and/or mild RHD were not as readily identified in the Kimberley as in FNQ. In FNQ, we observed a significantly greater proportion of ARF/mild RHD which may indicate that cases were being identified earlier here. Earlier identification would enable earlier intervention, including delivery of secondary prophylaxis to prevent the development or worsening of RHD, thereby ensuring that fewer patients progress to severe disease or require heart surgery. In Queensland, there was a centralised RHD control programme and a regional ARF/RHD database in place at the time of this study. This programme incorporated an ARF notification system, a centralised coordination unit, regular reminders to health providers about individuals requiring BP prophylaxis and specialist follow up, and ongoing training and support for health staff in relation to the management of ARF/RHD. In contrast, at the time, there was no such programme or regional ARF/RHD database in the Kimberley. This difference in the coordination of care may be associated with the differences in observed service delivery and disease severity between the two regions. An ARF/RHD-enhanced surveillance system similar to the one in place in FNQ has since been implemented in the Kimberley.

While we did demonstrate lower levels of echocardiography in ARF patients without RHD in the Kimberley, the use of echocardiography (and thus diagnosis and monitoring of severity) in those with RHD was comparable between regions. Differences in monitoring of disease severity alone do not explain the differences in disease severity observed.

More severe disease was associated with less delivery of secondary antibiotic prophylaxis and less specialist review in the Kimberley compared with FNQ. Even if the greater use of less effective oral antibiotic secondary prophylaxis\textsuperscript{23} in FNQ was excluded, 16% more of patients were prescribed BP prophylaxis and the median number of BP doses delivered was 75% greater in FNQ. Greater delivery of secondary antibiotic prophylaxis in FNQ would be expected to have led to fewer episodes of recurrent ARF, and hence, less disease progression. The recorded rate of recurrent ARF was, however, significantly higher in FNQ. Nonetheless, at the time of this study, ARF was a notifiable disease in FNQ, but not in the Kimberley, suggesting that episodes of recurrent ARF were more likely to be reported in FNQ and that significant underreporting and perhaps underrecognition was occurring in the Kimberley.

The delivery of specialist services observed in both the Kimberley and FNQ was less than optimal, with only 55.1% of RHD patients being reviewed within recommended time frames and 60.5% receiving a timely echocardiogram. An earlier study in the Kimberley reported that of those patients recommended visiting specialist or echocardiographic review, 78% and 64% attended respectively.\textsuperscript{11} Similarly, in the Northern Territory, while RHD patients with severe disease were usually receiving follow up, approximately half the people with moderate and mild disease had been inadequately investigated and/or had not received follow up.\textsuperscript{12}

RHD patients in FNQ were more likely to have been seen by a specialist within recommended time frames. This was confined to patients with RHD who had not undergone heart valve surgery (data not shown). More frequent specialist review in FNQ may have enhanced the uptake of secondary antibiotic prophylaxis and thus impeded the progression of disease, but it is not possible to confirm this. Despite more frequent specialist review in FNQ, by a workforce who provided contemporaneous echocardiography, and a centralised recall system, there was no difference in the delivery of echocardiography services to RHD patients in the Kimberley and FNQ. Indeed, Kimberley RHD patients with a history of valve surgery or other procedures were more likely to have
received a timely echocardiogram compared with FNQ patients. Specialist-provided echocardiography in FNQ, while apparently more frequently available, may have been deferred in busy clinics with other clinical priorities. A dedicated echocardiography service such as that used in the Kimberley is not subject to similar distraction and appears to have ensured those with more advanced disease had echocardiography performed as scheduled.

Many patients with advanced RHD, in particular those who have a mechanical valve in situ, require anticoagulation. Delivery of anticoagulation therapy to RHD patients was suboptimal. The lack of concordance between INR targets recommended by national guidelines and those recorded in patient notes is concerning, as is the finding that one-third of patients on warfarin did not receive adequate monitoring and that almost two-thirds of recorded INR results were outside recommended targets. A study in non-remote Australia found therapeutic anticoagulation in 57.6% of tests compared with 34.9% seen here. It is vital that initiatives be developed to address this issue in these remote Australian settings. Newer oral anticoagulants which do not require INR monitoring have been developed; however, evidence of their effectiveness in RHD, atrial fibrillation related to valvular disease and mechanical valves is lacking. Given the difficulties associated with anticoagulation and INR monitoring demonstrated here, balloon valvuloplasty, valve repair or bioprosthetic valve replacement are clearly preferable (where they are an option) for patients living in remote northern Australia.

While the differences in delivery of health services observed in this study, particularly the higher levels of BP monitoring and delivery and the more timely specialist review observed in FNQ, may be associated with the differing models of service delivery in the two regions, it is important to note that data were collected in the Kimberley in 2007 while data were collected in FNQ in 2008 and 2009. The national Australian guidelines for ARF and RHD diagnosis and management were published in 2006, and it is possible that one reason for improved concordance in FNQ was that the extra time between publication and audit in FNQ may have enabled the implementation of awareness programmes, education initiatives and system changes to align more closely with the guidelines.

Conclusion

This study has documented the nature, burden and management of ARF/RHD in two regions of northern Australia. We have demonstrated differences in disease severity that may, at least in part, be explained by differing levels of secondary prophylaxis uptake, differing specialist access and the presence or absence of a centralised ARF/RHD control programme. In both regions, specialist and echocardiography services, secondary prophylaxis and the management of anticoagulation have changed little over the last decade. Coordinated systems for ARF/ RHD management supported by centralised database and recall systems and a consolidated specialist healthcare team were associated with improved patient care and may partly account for fewer cases of severe disease and a reduced number of surgical and other interventions observed in FNQ.

Acknowledgements

The authors thank Ms Jacki Hopkins (Queensland Health), Ms Michelle Clark (RHD Australia Queensland) and Dr Carole Reeve (Kimberley Population Health Unit) for their assistance with data collection and project logistics. Graeme Maguire is supported by an NHMRC Practitioner Fellowship and the Margaret Ross Chair in Indigenous Health.

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Physiotherapy practice patterns for patients undergoing surgery for lung cancer: a survey of hospitals in Australia and New Zealand

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Key words
lungen neoplasm, physical therapy specialty, rehabilitation, healthcare survey, thoracic surgery.

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Received 7 May 2012; accepted 25 July 2012. doi:10.1111/j.1445-5994.2012.02928.x

Abstract

Background: There has been a recent increase in the research available to guide physiotherapy management of patients who require surgical resection for lung cancer. It is unclear whether this evidence has influenced clinical practice.

Aim: To describe physiotherapy practice patterns in the preoperative and postoperative management of patients who undergo surgical resection for lung cancer.

Methods: Physiotherapists involved in the management of patients who require surgical resection for lung cancer at hospitals across Australia and New Zealand were mailed a purpose-designed questionnaire.

Results: The response rate was 91% (43/47). Prior to surgery, 40% (n = 17) of the respondents indicated that patients were not assessed by a physiotherapist. In most hospitals (n = 39; 91%), patients did not participate in supervised exercise training before surgery. Most commonly, physiotherapy was commenced on the day following surgery (n = 39; 91%), with walking-based exercise being the treatment that was most frequently implemented in all patients (n = 40; 93%). Seventy-two per cent of respondents referred less than 25% of patients to pulmonary rehabilitation on discharge from hospital. Physiotherapy assessment and treatment choices were influenced predominantly by established practice in the hospital and personal experience rather than research findings.

Conclusion: In people who undergo surgical resection for lung cancer, physiotherapy services focused on reducing or preventing postoperative pulmonary complications. Despite recent data suggesting that exercise training is beneficial in this population, our data indicate that referral to pulmonary rehabilitation was uncommon.

Introduction

In Australia in 2007, more than 9000 cases of lung cancer were diagnosed.1 Cancers of the lung are the most commonly diagnosed cancers in men and the fourth most commonly diagnosed cancer in women. Throughout the world, they represent the leading cause of deaths from malignancy in both genders.2,3 Although surgical resection of the tumour is the treatment that offers the best chance of cure,4 this procedure is associated with important short and long-term impairments. Specifically, short-term postoperative complications include lung collapse, pneumonia and prolonged mechanical ventilation.5 Long-term impairments include reduced lung function and exercise capacity.6,7 Following resection, patients also report decreased health-related quality of life (HRQoL) when compared with healthy controls.8

Over the past 6 years, there has been an increase in publications pertaining to the effectiveness of physiotherapy for patients before and after surgery for lung cancer. Regarding preoperative management, two recent studies9,10 have reported that brief exercise programmes initiated prior to surgery served to decrease the length of hospital stay, suggesting reduced postoperative morbidity and healthcare cost. Regarding postoperative management, a randomised, controlled trial (RCT) conducted in...
New Zealand examined the effects of physiotherapy, which included breathing exercises, ambulation, and a progressive shoulder and thoracic cage mobility programme, on the incidence of pulmonary complications (i.e. pneumonia), intensive care unit readmissions and length of hospital stay in patients following lung resection. This study failed to demonstrate between-group differences (i.e. treatment vs control) probably because, at least in part, of an overall rate of postoperative pulmonary complications of less than 4% (3 out of 76 patients). However, with respect to exercise training following resection, it appears that a supervised programme of moderate intensity exercise in this population is feasible and safe, and may confer benefits in dyspnoea, exercise capacity and HRQoL, particularly among those who do not require concurrent chemotherapy. When commenced immediately following surgery, exercise training also assists with maintaining quadriceps muscle force.

Given the results of these recent publications, the aim of this study was to report current preoperative and postoperative physiotherapy practice patterns across hospitals in Australia and New Zealand for patients who require surgical resection for lung cancer. These results will extend those of Reeve et al., who described the physiotherapy management of patients undergoing thoracotomy in 2007. Of note, at the time their study was conducted there were very few data available to guide clinical practice. The current study will evaluate the extent to which findings of the recent studies in this area have been translated into clinical practice.

**Methods**

**Sample**

Hospitals in Australia and New Zealand that provide thoracic surgery and physiotherapy services were identified using Internet searches. That is, a list of major hospitals in Australia (http://en.wikipedia.org/wiki/List_of_hospitals_in_Australia) and New Zealand (http://en.wikipedia.org/wiki/List_of_hospitals_in_New_Zealand) was identified, and thereafter, individual hospital websites were examined to determine whether or not they provide thoracic surgery services. The list produced by this search was cross-referenced against one provided by the authors of a previous study. Inconsistencies in the eligible sites between the two lists were resolved by contacting the hospitals directly.

**Survey instrument**

A questionnaire (Supporting Information) was developed to collect information pertaining to characteristics of the hospitals and staff, the types of assessments completed prior to surgery, as well as physiotherapy management both before and after resection of lung cancer. The questionnaire was piloted by four experienced physiotherapists in order to optimise its face validity, readability and structure. Thereafter, the questionnaire was sent to two physiotherapists with a doctoral degree in the area of cardiorespiratory practice who were asked to comment on the layout, terminology and content. The final version of the questionnaire comprised three sections, consisted of 22 questions and took approximately 15 min to complete.

**Approach**

The Tailored Design Method (Dillman approach) was used, as it has been previously shown to reduce survey error and optimise response rate (RR). The first contact with each hospital was with the manager of the physiotherapy department through email. If no response was obtained within 4 weeks, a reminder email was sent, and this person was contacted through the telephone. The manager was asked to nominate the physiotherapist who had the most contact with patients who require thoracic surgery for lung cancer in their department (i.e. a senior cardiothoracic physiotherapist). Once identified, this physiotherapist was sent a letter (both through post and email) outlining the purpose and aims of the study. The questionnaire was then posted with a reply-paid envelope. For those who agreed to participate, 4 weeks were allowed for return of the questionnaire after which time a reminder letter was sent through email. Physiotherapists were asked not to answer questions if they were unsure of the correct response and were encouraged to contact other members of the healthcare team to seek information as appropriate. Where responses were not completed, the physiotherapist was contacted by telephone in an attempt to ascertain the most appropriate answer to each question.

Approval was granted from the Human Research Ethics Committee at Curtin University (approval number PT0185). Return of the questionnaire was taken as informed consent.

**Data analysis**

Responses were numerically coded for descriptive summaries and reporting of frequency. Analyses were undertaken using the Statistical Package for the Social Sciences (SPSS) version 19.0 (SPSS, Inc., Chicago, IL, USA).

**Results**

A total of 54 hospitals (46 in Australia and 8 in New Zealand) was deemed eligible to participate in the study.
Staff in the physiotherapy department at five hospitals did not respond to our repeated attempts to make contact (i.e. emails, faxing and phone calls). Hence, 49 questionnaires were mailed out (43 to hospitals in Australia and 6 to hospitals in New Zealand). Staff from two sites declined participation after receiving the questionnaire, as surgical resection for lung cancer was no longer performed at their facility. Of the 47 sites where both initial contact was made and surgical services for patients with lung cancer were provided, a total of 43 questionnaires was returned, yielding a RR of 91%. The four questionnaires that were not returned were all from private hospitals. Data pertaining to the distribution of hospitals are provided in Table 1.

**Characteristics of the physiotherapists and hospitals**

Most respondents (n = 35; 81%) had more than 5 years of clinical experience with 31 (72%) having more than 5 years of experience treating patients with respiratory diseases. Thirty-three (77%) respondents had completed their entry level qualification in Australia, with a smaller proportion from the United Kingdom (n = 5; 12%), New Zealand (n = 4; 9%) and the Republic of Ireland (n = 2; 5%). The majority of respondents held a bachelor’s degree as their highest tertiary qualification (n = 35; 84%). The number of patients with lung cancer who underwent surgery in the past month is shown in Table 2.

**Preoperative assessment, education and exercise training**

The majority of respondents stated that the most common assessments completed by patients prior to surgery were spirometry (n = 36; 84%) and computerised tomography (CT) scans (n = 31; 72%). Patients in 16 hospitals (37%) usually underwent measures of diffusing capacity for carbon monoxide (D_lCO), and five respondents (12%) stated that the cardiopulmonary exercise test (CPET) was routinely measured at their facility. Measures of HRQoL and 6-min walk distance were collected at two sites (5%), with the exercise responses through a stair climbing test and maximal respiratory pressures assessed at one hospital each. Eight respondents reported collecting ‘other’ measures such as blood tests, urine tests, the positron emission tomography scan, bronchoscopy/mediastinoscopy and CT-guided biopsy.

The involvement of the physiotherapists in the preoperative assessment and education of patients with lung cancer undergoing surgery is shown in Figure 1. In 40% (n = 17) of the hospitals, respondents indicated that patients were not assessed by a physiotherapist prior to resection for lung cancer. Nine respondents (21%) reported assessing all patients with lung cancer before surgery. When assessments were undertaken, common procedures comprised auscultation, cough, subjective reports of exercise tolerance and spirometry. Preoperative education was provided by physiotherapists to all of the patients in 19 hospitals (44%); the topics are summarised in Table 3.

### Table 1
Numbers and distribution of hospitals on a state-by-state basis

<table>
<thead>
<tr>
<th>State/island</th>
<th>Deemed eligible (n = 54)</th>
<th>Public/private (n = 35/19)</th>
<th>Responded to contact attempts (n = 49)</th>
<th>Declined participation† (n = 2)</th>
<th>Included in the analysis (n = 47)</th>
<th>Questionnaires returned (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>46</td>
<td>30/16</td>
<td>43</td>
<td>2</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>ACT</td>
<td>2</td>
<td>2/0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>NSW</td>
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<td>9/8</td>
<td>16</td>
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<td>13</td>
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<td>3/2</td>
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<td>5</td>
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<tr>
<td>NT</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>1/0</td>
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<td>0</td>
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<td>1</td>
</tr>
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<td>WA</td>
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<td>4</td>
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<td>SI</td>
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<td>2/0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

†Declined participation after receiving the questionnaire. ACT, Australian Capital Territory; NI, North Island; NSW, New South Wales; NT, Northern Territory; QLD, Queensland; SA, South Australia; SI, South Island; TAS, Tasmania; VIC, Victoria; WA, Western Australia; —, not applicable.

### Table 2
Number of patients with lung cancer who underwent surgery in the past month (n = 43)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Lobectomy, n (%)</th>
<th>Pneumonectomy, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>15 (35)</td>
<td>41 (95)</td>
</tr>
<tr>
<td>4–8</td>
<td>16 (37)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>9–12</td>
<td>5 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>5 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unsure</td>
<td>2 (5)</td>
<td>1 (2.5)</td>
</tr>
</tbody>
</table>
Four respondents (9%) reported that preoperative exercise training was provided in their hospitals to a 'few' patients. In these hospitals, it was most often the surgeon who initiated the referral.

**Postoperative management**

The majority of respondents (n = 39; 91%) reported that patients commenced physiotherapy on the first postoperative day, with four (9%) responding that patients were routinely treated on the day of surgery. Table 4 summarises the types of exercises/techniques implemented by physiotherapists as part of postoperative patient care. The most common treatments applied to all patients were walking exercises, cough/huff and breathing techniques. Following surgery, 40 respondents (93%) reported that all patients participated in walking exercise and in most facilities (n = 38; 88%), this was initiated as part of an early mobilisation programme by the physiotherapist. Cough/huff and breathing techniques were also used frequently as postoperative techniques for all patients (n = 36; 84% and n = 35; 81%, respectively). Of the 13 respondents (30%) that included 'other' exercises in the answer, 10 described shoulder range of motion and thoracic exercises as techniques undertaken by the physiotherapists.

Figure 2 shows the proportion of patients referred to outpatient exercise training programmes (pulmonary rehabilitation). Seventy-two per cent of respondents (n = 31) refer less than 25% of patients to pulmonary rehabilitation on discharge from hospital. Of these, two respondents mentioned that the existing pulmonary rehabilitation programmes in their region do not accept patients with a diagnosis other than chronic obstructive pulmonary disease.

Respondents were asked to indicate (on a 5-point Likert scale) which factors had most influenced their management of patients with lung cancer. The results are shown in Table 5.
Discussion

This survey detailed the current management and practice patterns of Australia’s and New Zealand’s physiotherapy services for people undergoing resection for lung cancer. The main findings were that: (i) prior to surgery, in 40% of the hospitals, patients were not assessed by a physiotherapist; (ii) the majority of respondents did not provide preoperative exercise training for patients with lung cancer; (iii) postoperatively, physiotherapy was most commonly commenced on the day following surgery, with walking-based exercise being the most frequently implemented treatment; and (iv) on discharge from hospital, 72% of respondents referred less than 25% of patients to pulmonary rehabilitation. Our RR of 91% is greater than that achieved by previous studies, conducted in the same countries, in the area of physiotherapy for patients following thoracic surgery.

Table 4 Types of exercises/techniques used following surgery

<table>
<thead>
<tr>
<th>Exercises/techniques, n (%)</th>
<th>Proportion of patients receiving the described exercises/techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None of them</td>
</tr>
<tr>
<td>Breathing techniques</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Airway clearance techniques (other than cough/huff)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Cough/huff</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Inspiratory muscle training</td>
<td>30 (70)</td>
</tr>
<tr>
<td>Aerobic (walking)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Aerobic (cycling)</td>
<td>29 (67)</td>
</tr>
<tr>
<td>Strength (lower limbs)</td>
<td>15 (35)</td>
</tr>
<tr>
<td>Strength (upper limbs)</td>
<td>20 (46)</td>
</tr>
<tr>
<td>Other†</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

†Other: the other topics mentioned were: shoulder range of movement and thoracic exercises (24%); posture re-education (23%); continuous positive airway pressure–non-invasive ventilation (2%) and stair climbing (2%).

Table 5 Factors influencing physiotherapy management of patients with lung cancer

<table>
<thead>
<tr>
<th>Influencing factor, n (n)</th>
<th>Not at all</th>
<th>A little</th>
<th>Somewhat</th>
<th>A lot</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>Published journal articles (n = 41)</td>
<td>0 (0)</td>
<td>8 (19)</td>
<td>18 (44)</td>
<td>13 (32)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Text books (n = 41)</td>
<td>3 (7)</td>
<td>14 (34)</td>
<td>15 (37)</td>
<td>5 (12)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Established practice in your hospital (n = 43)</td>
<td>0 (0)</td>
<td>4 (9)</td>
<td>12 (28)</td>
<td>15 (35)</td>
<td>12 (28)</td>
</tr>
<tr>
<td>Personal experience (n = 42)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>9 (21)</td>
<td>18 (43)</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Postgraduate education (n = 38)</td>
<td>12 (32)</td>
<td>7 (18)</td>
<td>14 (37)</td>
<td>4 (10)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Professional development (workshops, seminars, etc.) (n = 42)</td>
<td>4 (10)</td>
<td>6 (14)</td>
<td>21 (50)</td>
<td>8 (19)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Initial academic education (n = 41)</td>
<td>3 (7)</td>
<td>13 (32)</td>
<td>14 (34)</td>
<td>7 (17)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Other† please specify</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

†Other: protocol specified by the surgeon (twice) and intensive care consultant (once).
Physiotherapy practice in lung cancer

Preoperative assessment, education and exercise training

International guidelines\(^{21-24}\) recommend that the risk of perioperative and postoperative complications for those individuals who have a resectable tumour be based, at least in part, on measures of lung function and exercise capacity. Our finding that forced expiratory volume in 1 second (FEV\(_1\)) and D\(_{1}CO\) were the most commonly used preoperative assessments in this population is in agreement with these guidelines. The CPET is recommended to further refine the perioperative risk of surgery for patients with predicted postoperative values for either FEV\(_1\) or D\(_{1}CO\) of below 40%.\(^{21,22}\) Notably, a peak rate of oxygen uptake (<15 mL/kg/min appears to be a better predictor of postoperative complications than resting cardiac and pulmonary function.\(^{25,26}\) Notably, this measurement was collected in a small number of facilities (i.e. 12%).

The benefit of providing physiotherapy for patients prior to thoracic surgery is unclear. Educating patients before their surgery about the postoperative physiotherapy management appears to have no effect on the incidence of postoperative pulmonary complications.\(^{27}\) Nevertheless, our data suggest that 44% of the respondents provided preoperative education with respect to postoperative physiotherapy management.

The evidence for implementing physiotherapy treatment for patients prior to thoracic surgery is limited. Specifically, in patients awaiting surgery for lung cancer, Pehlivan et al.\(^{11}\) demonstrated that a 1-week package of physiotherapy treatment comprising breathing and coughing exercises as well as treadmill walking reduced the incidence of postoperative pulmonary complications (from 17% to 3%) and length of hospital stay (from 9.7 to 5.4 days) of patients with lung cancer compared with a control group that did not receive any preoperative physiotherapy. Although the study design precluded the determination of which physiotherapy intervention was responsible for the between-group differences, it is likely that treadmill walking was an important factor contributing to these results. That is, preoperative exercise training has been consistently shown to optimise exercise capacity in patients with lung cancer.\(^{28-30}\) and this may serve to minimise the incidence of postoperative pulmonary complications. Although implementing a programme of high-intensity exercise may be advantageous in this population, our data indicate that such services are offered by very few hospitals, data that concur with the findings of an earlier survey.\(^{17}\) Referrals to such programmes are likely to remain low because at least in part of the fact that patients would like their cancer to be removed as soon as possible.\(^{9}\) and delaying surgery by a few weeks until a programme of exercise training has been completed is unacceptable. Nevertheless, perhaps, there is a role for preoperative exercise training for those who have resectable tumours but are not eligible for surgery because of their poor exercise capacity.

Postoperative management

Early mobilisation and the use of upright position are established as best practice in the management of patients following major abdominal, cardiac or thoracic surgery.\(^{31}\) In keeping with this, most of the respondents reported early mobilisation and walking exercises as common postoperative treatments. The role of adding physiotherapy techniques, such as deep breathing exercises, to a programme of early mobilisation to minimise the incidence of postoperative pulmonary complications is controversial. A systematic review\(^{32}\) of 35 studies (13 RCT) concluded that there was little evidence for the effectiveness of respiratory physiotherapy in the prevention of pneumonia after abdominal surgery. Since this review, two high-quality RCT\(^{11,33}\) have explored the effect adding deep breathing exercises to a programme of early mobilisation following abdominal and thoracic surgeries. Neither study demonstrated an effect on preventing pulmonary complications. Nevertheless, it is important to note that the incidence of postoperative pulmonary complications and length of hospital stay in these two studies were both very low, and thus, the opportunity to confer a significant effect was limited. It is possible that such interventions are most appropriate for those who develop a postoperative pulmonary complication or have limited capacity to participate in early mobilisation. Our study suggests that most physiotherapists continue to implement breathing exercises frequently. This practice is likely to reflect a strong historical precedent for this treatment and is reflected in our data demonstrating that the single greatest influence on physiotherapists’ choice of treatment was the established practice at their hospitals and personal experience.

In addition to minimising the incidence of postoperative pulmonary complications, the physiotherapist plays an integral role in restoring the patient to their preoperative functional status. Evidence from a recent RCT\(^{34}\) demonstrated that a postoperative programme of shoulder exercises improved shoulder function and decreased
pain following open thoracotomy. Such a programme has yet to be implemented consistently given that only 24% of the respondents mentioned shoulder range of motion and thoracic range of movement exercises as techniques undertaken by the physiotherapists.

A low proportion of referrals to pulmonary rehabilitation after discharge was demonstrated by the current study. This may be due to both the lack of RCT of supervised exercise training following discharge from hospital after resection for lung cancer as well as the fact that pulmonary rehabilitation programmes focus on patients with respiratory conditions other than lung cancer. Nevertheless, over the past 6 years, several studies have been conducted to investigate the role of supervised exercise training for patients after surgery for lung cancer.\textsuperscript{15–19} They have demonstrated that exercise training is safe and feasible, and may confer benefits on exercise capacity and HRQoL. To date, one RCT has investigated the effects of exercise following surgical resection for lung cancer. In this study, the intervention group received twice daily strength and mobility training for the first 5 days after surgery followed by an additional 12 weeks of unsupervised home-based exercise.\textsuperscript{19} The control group received usual care that included airway clearance techniques, early ambulation and pain medication. The results showed that exercise assisted with maintaining quadriceps muscle force during the immediate postoperative period but was not associated with additional benefits in exercise capacity or HRQoL when reassessed 12 weeks following discharge. An important limitation of this study was the relatively minimal interaction with a healthcare professional during the home exercise programme (i.e. once a month over the 3-month programme) as well as the lack of standardisation of the home exercises (i.e. they were individualised according to patient hobbies). Further RCT are being performed to ascertain the effects of exercise training following surgery.\textsuperscript{5}

Limitations

The limitations of this study relate to those inherent within any survey of responder and recall bias. Our RR of 91\% suggests minimal responder bias. Further, inaccuracies related to recall bias were limited by: (i) ensuring that the questionnaire went to the physiotherapist who most frequently treated patients with lung cancer, (ii) instructing the respondents consult with other members of the healthcare team if they were unsure of the correct response, and (iii) following up with a phone call to address any perceived ambiguities in the questionnaire. For individual treatment approaches (e.g. walking-based exercise), we did not attempt to elicit specific prescription details, such as frequency, intensity or duration, as we believed that these variables were likely to vary considerably between patients within any given hospital.

Conclusions

This study has documented current physiotherapy practice patterns for patients with lung cancer undergoing surgical resection throughout Australia and New Zealand, and has demonstrated that physiotherapy services currently focus on minimising the immediate risk of postoperative pulmonary complications. Referral to pulmonary rehabilitation is uncommon for this patient population, and well-designed studies are needed to confirm the role of supervised exercise training in facilitating postoperative recovery in this patient population.

Acknowledgements

The authors thank Nola Cecins (Physiotherapy Department, Sir Charles Gairdner Hospital), Dr Kathy Stiller (Physiotherapy Department, Royal Adelaide Hospital), Carol Watson (Physiotherapy Department, Royal Perth Hospital), Jennifer Mackney (School of Health Sciences, The University of Newcastle), Dr Kevin Kemp-Smith (School of Physiotherapy, Curtin University) and Julien Graciet (Physiotherapy Department, Sir Charles Gairdner Hospital) for the support during the development and postage of the questionnaire, and Dr Julie C. Reeve (School of Physiotherapy, Faculty of Health and Environmental Studies, Auckland University of Technology) for kindly providing the list of hospitals from her previous study.

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**Supporting Information**

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

**Appendix**
Patterns of care for malignant pleural mesothelioma patients compensated by the Dust Diseases Board in New South Wales, Australia

S. C.-H. Kao, 1,2,3 S. Clarke, 4, 5 J. Vardy, 2, 3 P. Corte, 5 C. Clarke 1 and N. van Zandwijk 1, 3

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Key words
malignant pleural mesothelioma, pattern of care, chemotherapy, radiotherapy, extrapleural pneumonectomy, asbestos.

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Received 3 June 2012; accepted 5 August 2012.

Abstract
Background: The silent epidemic of mesothelioma in Australia is steadily increasing, and 30% of cases occur in New South Wales (NSW).

Aim: To describe the patterns of care and outcomes of patients with malignant pleural mesothelioma (MPM) in NSW.

Methods: MPM patients in NSW applying for compensation at the NSW Dust Diseases Board from 2007 to 2009 were included. Survival from time of diagnosis was determined by the Kaplan–Meier method. The Chi-squared test was used to determine if there was an association between utilisation of treatment and geographical location.

Results: A total of 138 patients was included: median age was 72.5; 91.3% male; 60.1% epithelial subtype; and 65.2% lived in major cities. All patients had at least one chest X-ray and computed tomography scan, and 21% had a positron emission tomography scan; 93.5% and 4.3% had histological or cytological confirmation respectively. Thoracoscopy (59.4%) was the most commonly used diagnostic procedure. Treatment utilisation: 53.6% chemotherapy; 35.5% radiotherapy; 9.4% extrapleural pneumonectomy (EPP); and 72.5% had palliative care involvement. There were no major differences in treatment utilisation between patients living in major cities and those in regional NSW (chemotherapy \( P = 0.42 \); radiotherapy \( P = 0.13 \) and palliative care \( P = 0.60 \)), except for a higher rate of EPP in regional patients (16.7% vs 5.6%; \( P = 0.03 \)). Median survival was 9.7 versus 12.3 months for city and regional patients respectively \( (P = 0.22) \).

Conclusion: Survival and treatment utilisation was not significantly different between MPM patients living in major cities and regional NSW, except for a higher rate of EPP in patients in regional NSW.

Introduction
Providing care to newly diagnosed patients with malignant pleural mesothelioma (MPM), which is almost always fatal, presents a significant challenge. Australia is among the countries with the highest national incidence of MPM. In 2007, 660 new cases were diagnosed; 30% of them were in New South Wales (NSW). This high incidence is the direct consequence of decades of heavy asbestos use in the previous century. It has recently become clear that exposure to asbestos in non-occupational settings is associated with an increased incidence of MPM. 3, 4

Reviewing 295 cases from the Australian Mesothelioma Program and Register treated in NSW teaching hospitals during the period 1980–1988. Driscoll et al. showed that 20% of patients were treated with chemotherapy and 20% received radiotherapy. 5 Contemporary data regarding treatment utilisation in NSW are not available. Furthermore, although evidence of geographical disparity for medical treatment utilisation and health outcomes has been reported in Australia, 6 there are no specific data for MPM.
By reviewing the databases of the NSW Dust Diseases Board (DDB) and Medicare Australia, we aimed to establish the diagnostic process, the treatment choices and the outcome of MPM patients compensated by the DDB in NSW. We also investigated if the residence of patients (regional vs major cities) influenced treatment choices and outcome, and we compared current medical practice in NSW with international standards/guidelines.7–9

**Materials and methods**

The study was approved by the Human Research Ethics Committee (HREC) at Concord Hospital. Study participants were MPM patients from NSW successfully applying for compensation at the DDB between March 2007 and March 2009. Written informed consent was obtained either from the patient or from the next-of-kin if the patient was deceased. HREC approved a waiver of consent in six patients where we were unable to identify a next-of-kin. Patients with peritoneal mesothelioma were excluded as the diagnostic process and treatments choices differ significantly from those for MPM.

The DDB provides compensation and covers the medical expenses of workers with dust diseases currently or previously employed in NSW (Workers’ Compensation (Dust Diseases) Act 1942). Compensation is awarded after the diagnosis is confirmed by the DDB Medical Authority, comprised of a panel of three respiratory physicians. Detailed clinical, radiological and pathological information as well as occupational histories and extent of asbestos exposure were reviewed. Survival outcome from death certificates (mandatory notification) and details of treatment reimbursed by the DDB were also available. Where information was incomplete or unavailable, we contacted treating physicians and hospitals and the Dust Diseases Tribunal and linked our data with Medicare Australia datasets.

Clinical stage was assessed by reviewing the computed tomography (CT) scans according to the American Joint Committee on Cancer staging criteria.10 The histological diagnosis and its subtype were taken from the pathology report and not routinely reviewed. In some cases, additional pathological review was carried out when requested by the DDB Medical Authority if there was doubt about the diagnosis.

The residential location of patients was classified into major cities, inner regional, outer regional, remote or very remote according to the Australian Standard Geographical Classification Remoteness Classification.11 For analyses, we grouped inner regional, outer regional, remote and very remote areas as regional NSW.

**International benchmarks**

Clinical practice in this study was compared with international benchmarks based on the European Society of Medical Oncology Clinical Practice Guidelines, British Thoracic Society Statement, and the Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons.7–9 These state that:

1. Chest X-ray (CXR) should be performed in all patients.
2. CT of the chest should be performed in all patients.
3. Histology is the gold standard in pathological diagnosis.
4. Immunohistochemistry (IHC) must be performed.
5. A minimum of four antibodies should be employed in the immunohistochemical assessment.
6. Histological subtype should be reported.
7. Clinical tumour stage should be recorded.
8. Thoracoscopy is the preferred method of obtaining diagnosis.
9. If chemotherapy is prescribed, a combination of platinum and an anti-folate drug should be used.
10. If radical surgery of extrapleural pneumonectomy (EPP) is proposed, it should take place within the context of multimodality treatment in a specialised thoracic centre.

**Statistics**

Overall survival (OS) from the date of histological diagnosis was determined by the Kaplan–Meier method, with results presented as median OS with 95% confidence intervals. The survival difference between patients in major cities and regional NSW, and treatment utilisation was examined using the log-rank test. The difference in the median duration of symptoms between patients living in major cities versus regional NSW was examined using the Mann–Whitney U-test. Descriptive statistics and the Chi-squared test were used to examine potential differences in treatment and outcome of patients living in major cities and regional NSW. A P-value of ≤0.05 was considered statistically significant. All analyses were performed using SPSS (SPSS, Chicago, IL, USA) for Windows version 17.0.

**Results**

A total of 138 MPM patients was included in this study of whom 126 (91.3%) were deceased. A further 98 patients or their next-of-kin declined to participate, and 34 patients were ineligible (Fig. 1). Baseline demographics are outlined in Table 1. The demographic characteristics of patients who declined to participate were similar.
Initial presentation was a pleural effusion in 127 patients (92%). The median interval between presentation with their first symptom and histological diagnosis (duration of symptoms) was 1.3 months (interquartile range: 0.4–3.9 months). The mean latency period (from initial asbestos exposure to histological diagnosis) was 45.7 years (standard deviation ± 40.4 years), and the median was 49.8 years.

### Diagnostic investigations

All patients had received at least one CXR and CT scan, while 29 patients (21%) had undergone positron emission tomography as part of imaging investigations.

Table 2 shows the procedures that led to the final diagnosis: 93.5% were based on a histological specimen; 4.3% were based on cytology. Three patients (2.2%) presented with typical clinical and radiological features of MPM, and no definite pathological diagnosis was made.

Most pathological diagnoses were made in conjunction with IHC (n = 130). The median number of diagnostic immunohistochemical stains used was 7 (range: 0–18); with calretinin (94.1%) the most commonly used mesothelial marker and carcinoembryonic antigen (71.1%) the most common carcinoma marker. In order of decreasing frequency, other mesothelial IHC markers included CK5/6, HBME1, WT1, thrombomodulin, D2-40 and mesothelin, and other IHC carcinoma markers used were TTF-1, BerEP4, CD15, MOC31, Tag 72.3, BG8 and L-cadherin.

### Treatment

Seventy-four patients (53.6%) received chemotherapy, and 49 patients (35.5%) received radiotherapy. Radical surgery was attempted in 13 patients (9.4%); 10 as part of a multimodality approach (Table 2).

Community and/or medical palliative care teams were involved in the care of 100 patients (72.5%).
Outcomes

The median survival was 10.6 months, and 6% survived 5 years or more. The median survival of patients who were considered fit for and who received chemotherapy was 15.7 months, compared with 5.4 months in those who were not considered fit for or who did not receive chemotherapy ($P < 0.001$). Likewise, patients who underwent radical surgery survived significantly longer than those who did not (median OS: 37.1 vs 9.7 months, respectively, $P = 0.001$). Survival did not seem to be affected by the prescription of radiotherapy (median OS: 13.6 vs 8.9 months for radiotherapy use and no radiotherapy, respectively, $P = 0.09$). Causes and the location of death are detailed in Table 3.

### Geographical variation in the pattern of care and outcome

There were no major differences between patients who resided in major cities or in regional NSW in the duration of symptoms (1.4 vs 1.1 months, respectively, $P = 0.82$), or in the distribution of clinical tumour stage (stage I-II: 39% vs 44%, respectively, $P = 0.59$). Significantly more patients from regional NSW received radical surgery than their counterparts living in cities ($P = 0.03$). Patients from major cities were more likely to die at their usual place of residence ($P = 0.02$), whereas regional patients were more likely to die in hospital (Table 4).

The Kaplan–Meier curves in Figure 2 reveal no significant difference in the survival of patients with different geographical background.

### International benchmarks

Table 5 summarises the proportion of patients in which the diagnostic process and treatment delivery met the international benchmarks. No significant differences in management were observed between patients from major cities and regional NSW.

### Discussion

We examined the pattern of diagnostic procedures, treatment utilisation and disease outcome in MPM patients in NSW, Australia, as a follow up to a report by Driscoll et al. dealing with patterns of care in MPM patients in the 1980s, when standard chemotherapy for MPM was not available. We evaluated if treatment

---

**Table 2** Diagnostic procedures and treatment received

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Diagnostic procedure (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>82 (59.4%)</td>
<td>Thoracoscopy</td>
</tr>
<tr>
<td>18 (13.0%)</td>
<td>Thoracotomy</td>
</tr>
<tr>
<td>25 (18.1%)</td>
<td>Radiology-guided procedures</td>
</tr>
<tr>
<td>4 (2.9%)</td>
<td>Chest wall biopsy</td>
</tr>
<tr>
<td>2 (1.4%)</td>
<td>Medical pleuroscopy (performed by respiratory physicians with sedation)</td>
</tr>
<tr>
<td>3 (2.2%)</td>
<td>Clinical pleural aspirate</td>
</tr>
<tr>
<td>1 (0.7%)</td>
<td>Axillary node dissection</td>
</tr>
<tr>
<td>1 (0.7%)</td>
<td>No procedures</td>
</tr>
<tr>
<td>2 (1.4%)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Chemotherapy intent (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (89.2%)</td>
<td>Palliative</td>
</tr>
<tr>
<td>6 (8.1%)</td>
<td>Neoadjuvant</td>
</tr>
<tr>
<td>2 (2.7%)</td>
<td>Adjuvant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency</th>
<th>First-line chemotherapy (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 (54.1%)</td>
<td>Carboplatin + pemetrexed</td>
</tr>
<tr>
<td>22 (29.7%)</td>
<td>Cisplatin + pemetrexed</td>
</tr>
<tr>
<td>2 (2.7%)</td>
<td>Pemetrexed</td>
</tr>
<tr>
<td>3 (4.1%)</td>
<td>Carboplatin + gemcitabine</td>
</tr>
<tr>
<td>1 (1.4%)</td>
<td>Cisplatin + gemcitabine</td>
</tr>
<tr>
<td>1 (1.4%)</td>
<td>Adriamycin</td>
</tr>
<tr>
<td>1 (1.4%)</td>
<td>Carboplatin, adriamycin + cyclophosphamide</td>
</tr>
<tr>
<td>4 (5.4%)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Radiotherapy (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 (40.8%)</td>
<td>Palliative intent (for symptom relief)</td>
</tr>
<tr>
<td>22 (44.9%)</td>
<td>Prophylactically to reduce recurrence in surgical tracts</td>
</tr>
<tr>
<td>7 (14.3%)</td>
<td>Adjuvant setting post EPP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency</th>
<th>EPP (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (23.1%)</td>
<td>EPP without other treatments</td>
</tr>
<tr>
<td>4 (30.8%)</td>
<td>Neoadjuvant chemotherapy + adjuvant radiotherapy</td>
</tr>
<tr>
<td>2 (15.4%)</td>
<td>Neoadjuvant chemotherapy alone</td>
</tr>
<tr>
<td>1 (7.7%)</td>
<td>Adjuvant radiotherapy + chemotherapy</td>
</tr>
<tr>
<td>2 (15.4%)</td>
<td>Adjuvant radiotherapy alone</td>
</tr>
<tr>
<td>1 (7.7%)</td>
<td>Adjuvant chemotherapy alone</td>
</tr>
</tbody>
</table>

EPP, extrapleural pneumonectomy.

---

**Table 3** Death-related details (n = 126)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct consequence of MPM</td>
<td>112 (88.9%)</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding/perforation</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Head injury/bleeding</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Respiratory failure post surgery</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Synchronous malignancy (gastric cancer)</td>
<td>1 (0.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Place of death</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>26 (20.6%)</td>
</tr>
<tr>
<td>Nursing home</td>
<td>8 (6.3%)</td>
</tr>
<tr>
<td>Dedicated hospice facility</td>
<td>38 (30.2%)</td>
</tr>
<tr>
<td>Public or private hospital wards</td>
<td>52 (41.3%)</td>
</tr>
<tr>
<td>Public hospital emergency department or intensive care unit</td>
<td>2 (1.6%)</td>
</tr>
</tbody>
</table>

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utilisation and patient outcomes differed due to geographical locations as there was concern that regionally domiciled patients may not have equivalent access to specialised diagnostic procedures and cancer treatment as city-based patients. When interpreting the data presented here, it is important to bear in mind that the cohort of patients presented was compensated by the DDB and virtually had no financial barriers to undergo intensive treatment, including travel cost to treatment centres.

Consistent with previous reports, we found a predominance of males, a relatively high median age at the time of diagnosis, and a median survival of close to 12 months. Compared with the NSW data from 1980s, our patients were older (median age 71 vs 64.1) and had a median survival almost 3 months longer (10.6 vs 8 months). Access to combination chemotherapy such as platinum and pemetrexed and combined modality treatment may have contributed to the improvement in survival, but lead-time bias might have also been a factor as the median time between the onset of symptoms and the diagnosis in our series is shorter (5 months in the 1980–1988 period vs 1.3 months in the 2007–2009 period). We hypothesised that this might be the consequence of improved awareness of the risk of disease among asbestos-exposed individuals and health service providers.

Another interesting observation was an increase of the latency period. In our series, the mean latency period was 45.7 years, which is 13 years longer than was recorded 20 years ago. Other studies have also found longer latency periods (of around 40 years), with one study reporting 59.2 years. The latency period presented here is consistent with an earlier DDB report that concluded that the latency interval had increased between 1972 and 2004. There are several potential reasons for this observation. First, earlier studies may have underestimated the latency period. However, if the latency period has truly lengthened, it may be related to increasing life expectancy and decreasing levels of asbestos exposure, as those at the greatest risk of developing MPM in a short period after asbestos exposure, either due to heavy asbestos exposure or due to personal predisposition, have developed MPM or died of other causes, and the affected individuals now may represent a different risk group. The frequency of the non-occupational exposure in our series

Table 4 Geographical variations in the pattern of treatment and outcome

<table>
<thead>
<tr>
<th></th>
<th>Major cities of NSW (n = 90)</th>
<th>Regional NSW (n = 48)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment received (n = 138)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Yes 46 (51.1%)</td>
<td>28 (58.3%)</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>No 44 (48.9%)</td>
<td>20 (41.7%)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>Yes 36 (40.0%)</td>
<td>13 (27.1%)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>No 54 (60.0%)</td>
<td>35 (72.9%)</td>
<td></td>
</tr>
<tr>
<td>EPP</td>
<td>Yes 5 (5.6%)</td>
<td>8 (16.7%)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>No 85 (94.4%)</td>
<td>40 (83.3%)</td>
<td></td>
</tr>
<tr>
<td>Palliative Care</td>
<td>Yes 71 (78.9%)</td>
<td>36 (75.0%)</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>No 19 (21.1%)</td>
<td>12 (25.0%)</td>
<td></td>
</tr>
<tr>
<td>Place of death (n = 126)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home/nursing home</td>
<td>28 (33.3%)</td>
<td>6 (14.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospice/hospital</td>
<td>56 (66.7%)</td>
<td>36 (85.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Percentages for active treatment do not add to 100% due to multiple modalities and non-treatment in some patients; EPP, extrapleural pneumonectomy; NSW, New South Wales.
confirms the concerns induced by a recent report from Western Australia showing an increasing incidence of mesothelioma after exposure to asbestos during home maintenance and renovations.\(^4\)

Evidence-based treatment approaches for MPM are limited, and the discussion of therapeutic proposals within a multidisciplinary setting is optimal.\(^7\)\(^-\)\(^9\) Platinum plus pemetrexed has become a widely accepted chemotherapy regimen for MPM, offering improvement in quality of life and a 3-month survival benefit.\(^2\)\(^1\)\(^,\)\(^2\)\(^2\) Radiotherapy has a role in palliating symptoms; however, its role for prophylaxis of tumour seeding in drain and surgical tracts remains controversial.\(^2\)\(^3\)\(^-\)\(^2\)\(^5\) The use of radical surgical approaches such as EPP has also remained controversial, as there is insufficient evidence from randomised studies available.\(^2\)\(^6\)\(^-\)\(^2\)\(^7\) Where a radical surgical approach is being sought, this should be carried out in the context of a multimodality setting in specialised centres.\(^7\)\(^-\)\(^9\)

We found a 53.6% utilisation rate for chemotherapy, 35.5% for radiotherapy and 9.4% for radical surgery. Treatment utilisation rates in NSW have clearly increased; between 1980 and 1988, only 20% of patients received chemotherapy, and 20% received radiotherapy, while no patients had EPP.\(^3\) Data from the Surveillance Epidemiology and End Results database in USA showed a 14% utilisation rate for radiotherapy, and 4% EPP for the period 1990–2004.\(^2\)\(^8\) and a 37% utilisation rate for chemotherapy between 1973 and 1984.\(^2\)\(^9\) A population-based overview capturing all mesothelioma diagnoses in British Columbia, Canada, between 1999 and 2005 demonstrated a chemotherapy utilisation rate of 41%.\(^3\)\(^0\) When the period was divided into 1999–2002 (pre-pemetrexed) and 2003–2005 (post-pemetrexed era), the utilisation rate increased from 31% to 61%. Another population-based study from Britain between 2002 and 2005 demonstrated an 18% utilisation rate for chemotherapy, 60% for prophylactic radiotherapy and 0% for radical surgery.\(^3\)\(^1\) In this study, 37% of patients presented with poor performance status, and only 37% of patients were considered fit for chemotherapy. Thus, it appears that internationally there is wide variation in treatment utilisation. In particular, the differences in utilisation of radical surgery may be due to the fact that radical surgery (as a part of combined modality treatment) has not been universally accepted as the standard of care. However, it is clear that the positive outcomes of chemotherapy clinical trials in the early 2000s have translated into clinical practice.

As the mainstay of MPM treatment is palliative, it is recommended that every patient should receive an early referral to a palliative care service.\(^6\) Although this study was not able to elucidate the timing of referral to palliative care services, 73% of patients in our series received a referral to palliative care. This rate is disappointingly low given most patients present with locally advanced disease and a high symptom burden.\(^3\)\(^2\) The importance of supportive/palliative care for ongoing symptom palliation from the time of diagnosis of patients with MPM was highlighted by the British Thoracic Society.\(^6\) There is also evidence that carers of patients with MPM value local palliative care service involvement earlier in the disease trajectory.\(^3\)\(^3\) In our series, we established if patients were referred and seen by palliative care services, but the exact services and the frequency and level of support received were not recorded. The relatively low rate of palliative care referral remains suboptimal and needs to be improved.

### Table 5  International benchmark

<table>
<thead>
<tr>
<th>Benchmark</th>
<th>Frequency of meeting the benchmark</th>
<th>Differences between major cities and regional Australia ((p)-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR performed ((n = 138))</td>
<td>138 (100%) 90 (100%) 48 (100%)</td>
<td>—</td>
</tr>
<tr>
<td>CT chest performed ((n = 138))</td>
<td>138 (100%) 90 (100%) 48 (100%)</td>
<td>—</td>
</tr>
<tr>
<td>Diagnosis based on histology ((n = 138))</td>
<td>129 (94%) 83 (92%) 46 (96%)</td>
<td>0.41</td>
</tr>
<tr>
<td>IHC performed for diagnosis ((n = 138))</td>
<td>130 (94%) 85 (94%) 45 (94%)</td>
<td>0.87</td>
</tr>
<tr>
<td>A minimum of four antibodies used for IHC ((n = 138))</td>
<td>127 (92%) 83 (92%) 44 (92%)</td>
<td>0.91</td>
</tr>
<tr>
<td>Histological subtype stated in pathology reports ((n = 138))</td>
<td>88 (64%) 56 (62%) 32 (67%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Clinical TNM stage recorded ((n = 138))</td>
<td>3 (2%) 2 (2%) 1 (2%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Thoracoscopy to obtain diagnosis ((n = 138))</td>
<td>82 (59%) 52 (58%) 30 (63%)</td>
<td>0.59</td>
</tr>
<tr>
<td>platinum + anti-folate drug used if chemotherapy indicated ((n = 74))</td>
<td>62 (84%) 40 (87%) 22 (79%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Multimodality treatment in specialised thoracic centres if EPP performed ((n = 13))</td>
<td>10 (77%) 4 (80%) 6 (75%)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

CT, computed tomography; CXR, chest X-ray; EPP, extrapleural pneumonectomy; IHC, immunohistochemistry; NSW, New South Wales; TNM, tumour, nodes, metastasis.
There is some evidence suggesting that Australian patients prefer to die at home. However, in our series, only 27% died at their usual residence. Interestingly, in the major cities, more patients died at their usual residence compared with their counterparts in regional Australia. The reasons for this difference are unclear, but the lack of resources to provide intensive in-house care in regional NSW could be an important factor.

It is reassuring that the disparity in health utilisation and survival outcome between city and regionally domiciled patients seen in other diseases was not apparent in MPM in NSW, although this may be due to treatment and transport to and from treatment being covered by the DDB. The treatment utilisation rates were not significantly different except for the use of radical surgery where more patients from regional NSW had the radical procedure. This difference is unexpected and may reflect a specific referral pattern of regional patients to specialised cardiothoracic centres.

The prolonged survival observed in patients receiving chemotherapy and radical surgery needs to be interpreted cautiously as selection bias may have played a role; that is, only fit patients with good performance status are likely to be offered chemotherapy and radical surgery. Unfortunately, we were unable to adjust our data by patient performance status, as this information was not available.

Our study confirms that diagnosis and treatment of MPM patients in NSW generally met international benchmarks, with two notable deficiencies: documentation of histological subtype by pathologists and documentation of clinical tumour stage. The International Mesothelioma Panel has recommended additional immunohistochemical stains to confirm the MPM diagnosis. An approach using a minimal panel of antibodies including calretinin, BG8 and CD15 has shown to be sufficient for the diagnosis of epithelial MPM. However, in this study, 6% of pathological diagnoses was not adequately confirmed by IHC.

The percentage of cases meeting the international benchmark did not seem to differ between patients in major cities or in regional NSW, giving further reassurance of the quality care received regardless of geographical location in NSW. To improve on the benchmark performance, a multidisciplinary team of experts from Australia is currently working on a national guideline for the diagnosis and treatment of MPM. The translation of the guidelines into clinical care is expected by 2013, after public consultation of draft guidelines as recommended by the National Health and Medical Research Council of Australia. A repeat of pattern of care study after implementation of the guidelines will assist in determining how successfully they are translated into practice.

As our patients were recruited from the DDB, the study population represents a selected sample and is biased towards patients who had occupational exposure. This is evident by the higher proportion of males (91.3%) compared with the national rate (84%) in 2007. Other limitations of the study are a relatively small sample size and a significant number who declined to participate (38%). Reassuringly, the patient characteristics of those who did not provide consent were similar to our study sample, but it is worth noting that our cohort represents only a third of the total NSW MPM cases ($n = 413$).

In addition, our study population is vetted by the DDB Medical Authority to establish the diagnosis of MPM. As a result, it is possible that DDB patients have additional diagnostic tests leading to an overestimation of compliance to the international guidelines related to the diagnostic process. Furthermore, as mentioned previously, patients in this study have access to DDB compensation and reimbursement of medical expenses, and this could well influence the patient’s capacity to access specialised treatments, hence overestimating the treatment utilisation and outcome compared with the general MPM population.

Conclusion

We have established a contemporary picture of the diagnostic process, treatment choices and outcome of MPM patients compensated by DDB in NSW. Comparing our findings with the 1980s NSW data, patients were older, tended to have shorter time between the onset of symptoms and diagnosis, and had increased treatment utilisation and longer survival. Apart from a higher rate of EPP in regional NSW, there did not appear to be differences in the pattern of diagnosis, treatment and survival outcome, as well as the proportion of cases meeting the international benchmarks for MPM patients diagnosed in major cities or in regional NSW. Although these findings demonstrate the feasibility of delivering equivalent care in regional NSW, there remains room for improvement in the management of MPM. It is hoped that national guidelines for the diagnosis and treatment of MPM will further enhance the outcome of patients by optimising medical care.

Acknowledgements

We sincerely thank Kirsty Hannaford-Turner, Amanda Ellis, Giles Yates (Workers’ Compensation Dust Diseases Board NSW) and Victoria Keena (Asbestos Diseases Research Institute) who made this project possible. We also thank the Dust Diseases Tribunal for their assistance in this project.
Pattern of care for mesothelioma


References


Screening and management of renal disease in human immunodeficiency virus-infected patients in Australia

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Key words
clinical immunology, clinical nephrology, chronic kidney disease, HIV infection.

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Received 23 April 2012; accepted 18 August 2012.


Abstract

Background: Renal disease has become one of the most important comorbidities observed in the human immunodeficiency virus (HIV)-infected patient cohort. Data are lacking on the current screening and management of renal disease in patients with HIV. We evaluated HIV-infected Australian adults in primary care to determine current practices.

Methods: This prospective, multicentre observational study included two rounds of data collection; the first was followed by an educational programme. Outcomes included screening for renal disease; management of risk factors for kidney disease and other comorbidities associated with renal disease.

Results: Fifty-three general practitioners participated with 733 patients enrolled. Most were male (94%); almost 40% were 41–50 years of age, and 6% and 84% were receiving antiretroviral therapy. Comorbidities were common; 19% had hypertension, 5% were diabetic, 32% were dyslipidaemic, and 40% were smokers. Estimated glomerular filtration rate was commonly measured in both rounds of data collection (96% vs 95%). Proteinuria was assessed less frequently; this improved after education (48% vs 71%). Almost 10% of patients tested had proteinuria on urinalysis. Of the 45 patients (6%) with renal impairment (estimated glomerular filtration rate <60 mL/min), none was referred for assessment by a renal specialist.

Conclusions: This large observational study provides important information on renal disease in HIV-infected patients, an area with a paucity of clinical data. Current screening and management practices fall short of suggested guidelines. Failure to refer patients to specialists is a major deficiency. Improvements with education suggest the need to promote awareness of guidelines in primary care doctors.

Introduction

With improved survival afforded by modern antiretrovirals (ARV), chronic complications of human immunodeficiency virus (HIV) infection, including cardiovascular (CV), liver and renal diseases, have emerged as major...
causes of morbidity and mortality in HIV infection. Highly active ARV therapy (ART) has changed the pattern of renal disease observed among patients with HIV infection. The incidence of HIV-related diseases, such as HIV-associated nephropathy (HIVAN), has declined substantially, although the overall incidence of renal disease has not decreased. Renal function may be abnormal in up to 30% of patients; however, this is often not recognised clinically. Comorbidities such as hypertension and diabetes, ageing, and ARV medications may account for the preponderance of renal disease among this population. Among HIV-infected patients, proteinuria and abnormal renal function are both associated with progression of HIV infection and increased mortality. As well, the burden of renal disease is likely to escalate, with HIV a chronic disease and the age of the Australian population projected to increase dramatically. All patients with newly diagnosed HIV infection are at risk for renal disease, but there are limited data concerning the patterns of change of renal comorbidities among HIV patients, as well information regarding screening and management of kidney disease in primary practice.

Screening for renal disease is recommended in all HIV-infected patients. Early detection of renal disease and early intervention may slow or halt the decline towards end-stage renal failure (ESRF). Individuals with indicators of renal disease (proteinuria, haematuria or a reduced estimated glomerular filtration rate (eGFR)) are at an increased risk of ESRF. Among people living with HIV infection, controlled studies examining the effects of classical risk factors for kidney disease in the non-HIV-infected population are lacking, as are specific trials examining the effects of risk factor intervention and screening. As well, the modified diet in renal disease (MDRD) equation used to calculate the eGFR has not been validated in the HIV-infected cohort. However, the need for early detection is well established in the general population, and its importance may be increased, given the high burden of renal disease among HIV-infected patients.

The extent of the problem of renal disease among people with HIV infection in Australia is unknown. Patients with existing renal disease or HIV are usually excluded from clinical trials. The development of public health strategies for the prevention and management of renal disease in this group requires appropriate population-based information. In Australia, general practitioners (GP) play a significant role in the management of patients with HIV infection and in the screening and management of chronic kidney disease (CKD). Over the past decade, guidelines have been formulated for clinical management of risk factors in the general population. Only recently, however, guidelines for the management of renal disease in people with HIV have been published based on data extrapolated from the general population as well as from observational studies in the HIV-infected cohort.

This study was undertaken to address the complete lack of data available in this area. It is one of the largest population-based studies of renal disease undertaken in the HIV-infected cohort at the primary practice level. This observational study provides important information to improve the understanding of the prevalence of renal disease, current screening and management practices, and the extent of comorbidities seen in this patient population.

**Methods**

This was a prospective, multicentre study to assess the adherence of Australian physicians to national and international guidelines for the screening and management of CKD in adults (≥18 years) with HIV infection. It was conducted between May 2009 and March 2010 with GP prescribers of HIV medicines. These prescribers participate in the Australasian Society for HIV Medicine (ASHM) mentoring programme and engage in continuing medical education relevant to the use of drugs for the management of HIV. HIV medicines are specialised pharmaceuticals that are subsidised under the Australian government’s Pharmaceutical Benefits Scheme; prescription of these medicines is limited to specialist providers. The study was based on the Royal Australian College of General Practitioners (RACGP) clinical audit design.

**Data collection**

Invitations to participate were sent to all GP registered with ASHM through email and mail. GP who participated obtained informed consent from a minimum of 10 consecutive HIV-infected patients. Patients eligible for inclusion in the study were all those patients attending the practice who were infected with HIV regardless of whether or not they were on antiviral treatment and regardless of the severity and extent of the underlying disease and associated complications. The GP entered data relevant to screening and management of renal risk factors online. Two rounds of data collection were undertaken 6 months apart. After the first round of data collection, GP were provided with feedback about how they screened and managed renal risk factors in their patients compared with pooled results and guideline recommendations. An educational programme was also undertaken, including use of educational materials, clinical meetings and conferences. Follow-up data assessed
overall changes screening and management of renal risk factors, and the effectiveness of the educational intervention.

**Study variables**

The study included demographical information, relevant medications and data required to assess renal health according to national and international standards. This comprised use of investigations for renal disease (dipstick urinalysis, eGFR), assessment for HIV-associated risk factors for kidney disease (hepatitis C infection, CD4+ cell count <200 cells/mL, HIV RNA viral load >4000 copies/mL) and assessment for other risk factors associated with kidney disease in the general population, including blood pressure (BP), blood glucose, use of nephrotoxic medications, smoking, lipid profile and CV risk (Framingham Risk Equation over 10 years) calculations. The provision of lifestyle advice, including smoking cessation, dietary and alcohol advice, and physical activity, was determined.

eGFR was estimated using the modified MDRD equation. Participants were categorised based on eGFR into normal renal function (≥60 mL/min per 1.73 m²) or renal impairment (<60 mL/min per 1.73 m²). Hyper tension was defined as systolic BP greater than or equal to 140 mmHg or diastolic BP greater than or equal to 90 mmHg. Hyperlipidaemia was defined as total cholesterol (TC) >6.0 mmol/L or low-density lipoprotein cholesterol >4.0 mmol/L. Diabetes mellitus was defined as a self-reported diagnosis of diabetes mellitus on hypoglycaemic therapy or fasting plasma glucose ≥7.0 mmol/L or 2-h plasma glucose ≥11.1 mmol/L. Current smoking was defined as smoking regularly or ceased within the previous 12 months.

**Statistical analysis**

Analysis of the audit data was overseen by the steering committee. Comparison of proportions was made using Chi-squared tests for equal proportion or Fisher’s exact tests where numbers were small with results reported as numbers (percentages). A two-sided \( P \)-value of 0.05 was considered to be statistically significant. All analysis was performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

**Ethical approval**

The study received ethics approval from the RACGP National Research and Evaluation Ethics Committee. The study was approved by the RACGP Quality Assurance and Continuing Professional Development programme for 2008–2010 and was endorsed as continuing medical education activity for HIV practitioners.

**Results**

Between May 2009 and March 2010, 53 GP reported information relating to renal and CV risk management in a convenience sample of their HIV-infected cohort \((n = 733)\). Table 1 shows the composition of patients with respect to demographical and clinical characteristics. The majority (94%) were male, almost 40% were aged 41–50 years of age, 88% were Caucasian, 6% were coinfected with hepatitis C virus, and 84% of patients were receiving ART.

Comorbidities were common; 35% were smokers, 36% were overweight, and hypertension or hyperlipidaemia was present in 19% and 32% of individuals respectively. Six per cent of patients were known to have established CV disease. Twenty-five per cent of patients with hypertension who, by management guideline definition, were eligible for therapy were not being treated. Additionally, 16% of patients in this study did not have a BP measurement in their medical record. BP was greater than 140/90 mmHg in 7% of patients with known BP readings. Of the 228 patients with hyperlipidaemia, 45% were not receiving lipid-lowering medications. TC greater than 5 mmol/L was found in 54% of patients with cholesterol measurements. Five per cent of patients in this study were known to be diabetic. However, only 40% of patients had ever had a fasting blood sugar measurement performed, and of those, 12% were greater than 6 mmol/L.

Guidelines recommend that screening for renal disease should be performed at baseline and at least annually thereafter and include an assessment of eGFR and urinalysis. The estimation of renal function by GP is shown in Table 2. Routine estimation of glomerular filtration rate (GFR) was common in both rounds of data collection (96% vs 95%), and in 45 (6%) patients, eGFR values were less than 60 mL/min. Of those 45 patients with an eGFR less than 60 mL/min, all had risk factors for renal disease, such as hypertension, diabetes or use of nephrotoxic medications, and 42 (93%) of these patients had at least +1 proteinuria. However, none of these patients had ever been referred to a renal physician. A minority of those patients with renal impairment had ever undergone renal ultrasonography. An eGFR <60 mL/min was more likely to be associated with age >60 (26% vs 8%, \( P = 0.003 \)), ART for 1–5 years (70% vs 47%, \( P = 0.03 \)) and a family history of kidney disease (13% vs 1%, \( P < 0.0001 \)). Of those patients ever screened for proteinuria with urinalysis \((n = 382, 52\%)\), almost 10% demonstrated at least +1 proteinuria. As well, only
30% of the patients in this study had undergone urinalysis in the past year. Of those patients with proteinuria, only 41% had their protein excretion quantitated. Encouragingly, physician adherence to renal assessment recommendations improved considerably during this study. The incidence of dipstick urinalysis and testing for protein/creatinine ratio both improved significantly in the second round of data collection (\( P < 0.0001 \) for both).

Overall, physicians were more likely to perform a dipstick urinalysis in patients taking tenofovir (54% vs 43%, \( P = 0.006 \)) or abacavir (32% vs 22%, \( P = 0.006 \)). Patients who received a dipstick urinalysis were also more likely to receive advice regarding physical activity (80% vs 60%, \( P < 0.0001 \)) and a healthy diet (84% vs 68%, \( P < 0.0001 \)). However, despite the increased use of screening investigations, the number of patients referred for specialist renal assessment did not increase.

Discussion

This study has demonstrated that renal disease is common in the HIV-infected population in Australia and that current screening and management of CKD at the primary practice level is inadequate, falling well short of suggested clinical practice. There are, at present, limited data available specific to the HIV population, and many guidelines and suggestions for clinical care of CKD in this population are

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>All (n = 733)</th>
<th>Round 1 (n = 530)</th>
<th>Round 2 (n = 203)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>687 (94)</td>
<td>493 (93)</td>
<td>194 (96)</td>
<td>NS</td>
</tr>
<tr>
<td>18–30 years</td>
<td>40 (5)</td>
<td>33 (6)</td>
<td>7 (3)</td>
<td>NS</td>
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<tr>
<td>31–40 years</td>
<td>180 (25)</td>
<td>133 (25)</td>
<td>47 (23)</td>
<td>NS</td>
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<tr>
<td>41–50 years</td>
<td>285 (39)</td>
<td>133 (25)</td>
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<td>51–60 years</td>
<td>162 (22)</td>
<td>117 (22)</td>
<td>45 (22)</td>
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<td>60+ years</td>
<td>64 (9)</td>
<td>43 (8)</td>
<td>21 (10)</td>
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<td>Caucasian</td>
<td>644 (88)</td>
<td>465 (88)</td>
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</tr>
<tr>
<td>HCV coinfection</td>
<td>41 (6)</td>
<td>28 (5)</td>
<td>13 (6)</td>
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<tr>
<td>HIV RNA viral load &gt;4000 c/mL</td>
<td>74 (10)</td>
<td>61 (12)</td>
<td>13 (6)</td>
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<td>CD4+ cell count &lt;200 c/mm²</td>
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<td>14 (3)</td>
<td>7 (3)</td>
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<td>47 (6)</td>
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<td>16 (8)</td>
<td>NS</td>
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<td>Diabetes</td>
<td>40 (5)</td>
<td>29 (5)</td>
<td>11 (6)</td>
<td>NS</td>
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<tr>
<td>Smoker</td>
<td>261 (36)</td>
<td>200 (38)</td>
<td>61 (30)</td>
<td>0.05</td>
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<tr>
<td>Overweight or obese</td>
<td>223 (30)</td>
<td>153 (29)</td>
<td>70 (34)</td>
<td>NS</td>
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<tr>
<td>Hypertension†</td>
<td>136 (28)</td>
<td>104 (28)</td>
<td>32 (29)</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidaemia‡</td>
<td>115 (29)</td>
<td>85 (29)</td>
<td>30 (29)</td>
<td>NS</td>
</tr>
</tbody>
</table>

†Defined as a BP >140/90 mmHg. ‡Defined as TC >6.0 mmol/L. BP, blood pressure; CVD, cardiovascular disease; HCV, hepatitis C virus; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NS, not statistically significant; TC, total cholesterol; Tx, treatment.
extrapolated from studies performed in the HIV-negative cohort. Indeed, the routinely used eGFR used to estimate renal function in the general population has not been validated among HIV-infected individuals.\(^1\) Despite this and because of the high risk of kidney disease observed in patients with HIV infection, estimation of kidney function is likely to be an important component of their care. A suggested approach to the screening and management of renal disease among HIV-infected patients provided to GP as part of the educational programme in this study is shown in Figure 1. This study demonstrated that estimation of eGFR by GP is common, but none of the patients in this study with a reduced eGFR had ever seen a renal physician. The high level of other comorbidities, use of nephrotoxic medications and the low level of further investigations performed to evaluate this renal dysfunction would suggest that the management of established renal impairment among these patients is suboptimal. Specialist referral of patients with risk factors and stage 3 CKD (eGFR is <60 mL/min) is recommended\(^2\) but not used in our study; the reasons for this require further evaluation.

Kidney function is recommended to be measured at least annually in patients with HIV, with more frequent screening recommended in many circumstances.\(^1\) eGFR had been estimated in more than 90% of the patients. This compares favourably to a previous study of kidney disease by GP in patients with type 2 diabetes.\(^2\) Even mild impairment of GFR is associated with an increased CV risk\(^26,27\) and increased mortality rate among the general population.\(^28,29\) The death rate following CKD in the HIV-infected population is also increased.\(^30\) Awareness of a reduced GFR is also important to enable targeting of CV risk factors and treatment of hypertension, leading to slowing in the progression of kidney damage among the non-HIV-infected population. Renal impairment is also associated with progression of HIV infection and mortality in the HIV-infected patient group.\(^8\) Reduced GFR also has significant implications for drug prescription and drug toxicities.\(^31,32\)

The assessment of proteinuria by urinalysis in only 52% of patients did not meet national\(^2\) or international guidelines.\(^11\) These guidelines are based primarily on data derived from randomised studies among non-HIV-infected populations, particularly patients with diabetes. Randomised studies among HIV-infected patients are needed to ensure the applicability of these data to this population. Currently, these trials are lacking, and data from HIV-infected patients are derived only from observational studies. However, in our study, of those screened, almost 10% of patients demonstrated significant levels of proteinuria (at least +1), a proportion lower than in previous reports.\(^4,5\) This may be partially explained by differences in patient populations and era of treatment. The majority of patients included in this study were Caucasian, meaning HIVAN, a disease almost exclusively of black African or Afro-Caribbean patients,\(^13\) was uncommon within this cohort. Most patients had no further investigations to evaluate their proteinuria, and none were referred to renal physicians.

In the general population, those with proteinuria have a 14-fold relative risk of ESRF during 10 years of follow-up.\(^11\) In those with established renal disease, proteinuria is an important predictor of the risk of progression\(^34\) and mortality.\(^57\) Data from controlled studies in the HIV-infected population to assess the specific effects of proteinuria among this patient population are lacking, but uncontrolled studies suggest that angiotensin-converting enzyme inhibitors may be beneficial for patients with HIVAN. However, controlled trials examining the more widespread use of antiproteinuric agents in HIV-infected patients without HIVAN do not presently exist.\(^6\) Given that mortality rates in patients with HIV infection and CKD are higher than those observed in age- and sex-matched controls with similar degrees of renal dysfunction,\(^30\) regular screening in this cohort is particularly important. The low incidence of screening for proteinuria among GP highlights the need for further education and other interventions to improve screening practices.

Classical risk factors for kidney disease in the general population are well established and include hypertension, diabetes, age and smoking. These risk factors are prevalent among individuals infected with HIV, for
example, the prevalence of hypertension among HIV-infected persons has been estimated at between 12% and 34%.²,³,³⁶,³⁷ In general, the demographics of our cohort was comparable with that reported by the Australian HIV Observational Database (AHOD)³⁸ and revealed a similar prevalence of risk factors for kidney disease. HIV-specific randomised, controlled studies are needed in this area to confirm the applicability of these risk factors to the HIV-infected population. However, the high prevalence of these risk factors seen in our study highlights the need for adequate screening and early detection of kidney disease in this at-risk population.

In our study, 25% of patients with hypertension who, by guideline definition, were eligible for therapy were not being treated, and 65% of the 115 patients with hyperlipidaemia were not receiving lipid-lowering medications. As yet, there are no randomised, controlled trials that confirm the beneficial effect of risk factor management on renal disease specifically in those with HIV infection. As well, those patients with HIV and kidney disease are excluded from many current clinical trial protocols. However, risk factor intervention for primary prevention is warranted in the HIV population given the high burden of risk. Efforts to improve the use of BP and lipid-lowering drugs in those who fulfil current guideline criteria should remain a priority.

The use of potentially nephrotoxic medications was relatively common, even among those patients with renal impairment or risk factors for renal disease. Additionally, almost half of all patients were on the potentially nephrotoxic nucleotide analogue reverse transcriptase inhibitor tenofovir disoproxil fumarate (TDF). The reported prevalence of significant TDF-associated renal toxicity in cohort studies is variable (0.3–2%).³⁹,⁴⁰ We found no statistically significant difference related to TDF use in the incidence of CKD among the patients in our study.

This study has a number of limitations. The patient sample is biased towards patients who regularly attend their GP and to GP with a greater interest in participation. Although every effort was made to ensure a representative distribution of general practices, selection bias in relation to participating investigators and enrolled patients cannot be excluded. However, the demographics in our study corresponded to those observed in the AHOD Annual Report.³⁸ It would also have been ideal to include all specialist primary practice providers of HIV care in the study; this was not possible as it was not mandated as part of their continuing educational programme. The recruitment into the study by provider interest may limit the applicability of these results and lead to an underestimation of suboptimal screening and management practices in the GP overall. The smaller sample size in the second round of data collection may have reflected bias in selection of patients and possibly magnified the apparent response to education of the GP.

Conclusion

The present study contributes important information to the area examining current screening and management practices of CKD in the HIV-infected patient population at the primary practice level. There is a high prevalence of risk factors for renal disease, as well as significant levels of proteinuria and renal impairment among Australian adults with HIV infection. Assessment of renal function falls short of national and international guidelines, particularly with regards to referral to renal physicians. While we await the results of studies of risk factor intervention in HIV-infected adults, there remains potential to improve screening and management practices for renal disease among this population.

References


Extra-pancreatic manifestations of IgG4-related systemic disease: a single-centre experience of treatment with combined immunosuppression

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Abstract

Background/Aim: IgG4-related systemic disease (IgG4-RSD) is a systemic inflammatory disease distinguished by tissue infiltrates of IgG4+ plasma cells and elevated serum IgG4 levels. While IgG4-RSD often involves the pancreas, extra-pancreatic organs are also frequently affected. Here, we review the presentation and management of patients with extra-pancreatic IgG4-RSD.

Methods: A retrospective analysis was performed on patients diagnosed with extra-pancreatic IgG4-RSD identified from a single centre.

Results: Six patients with extra-pancreatic IgG4-RSD were identified. The median age of the patients was 64 years. The range of involved organs included lymph nodes (three patients), ocular adnexa, lung, kidneys, meninges and exocrine glands. The median delay in diagnosis was 13.5 months (4–60 months). Four patients had elevated serum IgG4 levels at diagnosis. Five symptomatic patients were commenced on combination immunosuppression, which included corticosteroids. Maintenance therapy with azathioprine was used in one patient, methotrexate and mycophenolate were each used in two patients, and cyclophosphamide in one patient. Four treated patients went into remission, while two patients had persistent radiological disease. One patient experienced two relapses.

Conclusion: IgG4-RSD can manifest in a variety of organs. Lack of awareness regarding this entity may delay diagnosis. Combination treatment of corticosteroids and conventional immunosuppression is effective.

Introduction

IgG4-related systemic disease (IgG4-RSD; also referred to as IgG4-multiorgan lymphoproliferative syndrome (IgG4-MOLPS))1 is an inflammatory disease first recognised in the lesions of patients with type 1 autoimmune pancreatitis (AIP).2,3 The same pathological findings were subsequently identified in several extra-pancreatic organs, such as liver, lymph nodes and aorta, as well as being described in the lesions of previously unexplained chronic inflammatory diseases, such as retroperitoneal fibrosis, Riedel thyroiditis, Mikulicz chronic sclerosing dacryoadenitis of the lacrimal glands and Kuttner chronic sclerosing sialadenitis of the salivary glands.4 Regardless of location, IgG4-RSD is characterised by tissue infiltration with polyclonal IgG4+ plasma cells and lymphocytes with associated fibrosis.1 Corticosteroids are the established treatment for patients with pancreatic involvement.5,6 While there have been positive reports of corticosteroid treatment for extra-pancreatic IgG4-RSD, the optimal treatment regimen is less established.2 We report on the treatment of six patients with extra-pancreatic IgG4-RSD with corticosteroid and conventional immunosuppressive drugs.

Methods

Cases and diagnosis of IgG4

Cases of confirmed extra-pancreatic IgG4-RSD seen in the clinical immunology department of Westmead Hospital between 2007 and 2010 were reviewed in association with the patients’ medical histories, histopathology and imaging results. Cases of IgG4-RSD confined to the pancreas were excluded. The medical files were reviewed for data on clinical symptoms prior to a
confirmed diagnosis of IgG4-RSD, duration of medical therapy, age, sex, volunteered ethnicity and comorbid medical conditions.

**IgG4 quantitation**

Serum IgG4 measurements at diagnosis were available for four of six patients. All measurements were performed on an IMMAGE nephelometer (Beckman Coulter Australia Pty Ltd, Gladesville, NSW, Australia), with a 3% coefficient of variation.

**Immunohistochemistry**

Immunohistochemistry was performed after heat-induced antigen retrieval with a mouse monoclonal antibody against human IgG4 (Zymed Laboratories, clone HP6025), followed by development with the automated Ventana Universal dianminobenzidine tetrahydrochloride (DAB) detection kit (Ventana Medical Systems, Tucson, AZ, USA). For each case, the number of IgG4⁺ plasma cells was manually counted in several non-overlapping high-power fields (HPF; × 40 magnification). A diagnosis of IgG4-RSD was confirmed in the presence of (i) histopathological findings of a lymphoplasmacytic infiltrate, storiform fibrosis, sclerosis and obliterative phlebitis in affected organs; (ii) an absolute number of IgG4-positive plasma cells > 50 per HPF; and (iii) a percentage of IgG4⁺ to IgG⁺ cells > 40%.

**Results**

**Patient demographics**

We identified six adult patients (four females) with extra-pancreatic IgG4-RSD disease between 2007 and 2010 (Table 1). Two patients had been previously reported – patient 1 after 8 weeks of treatment only, and patient 4 with AIP only. This report extends patient 1’s observations to 72 months and extends patient 4’s observations to include subsequent renal IgG4-RSD. The median age of the patients was 64.8 years (range from 51 to 72 years). In these six patients, the median time to diagnosis was 13.5 months from initial presentation (range 4–60 months). The median length of follow up after diagnosis was 15 months (range 10–72 months).

**Extra-pancreatic IgG4-RSD can occur without pancreatic disease**

Extra-pancreatic IgG4-RSD occurred in the exocrine glands (lacrimal, parotid and salivary), orbit, lymph nodes, lungs, kidneys and meninges (Fig. 1). Four patients had no clinical, biochemical or computed tomography (CT) evidence of pancreatic involvement. In contrast, patient 1 developed a single episode of pancreatitis (abdominal pain and an elevated lipase of 1410 U/L (normal range NR < 110)) without CT evidence of AIP, and patient 4 had been diagnosed with AIP 2 years prior to renal involvement.

**Specific organ involvement**

Our cohort mostly had symptomatic subacute involvement of a variety of organs (Table 1):

- Lymphadenopathy was the most common extra-pancreatic manifestation. Concurrent lymphadenopathy was present with IgG4-related lacrimal and pancreatic disease in patients 1 and 4 respectively. Patient 3 had asymptomatic multifocal lymphadenopathy (up to 1.6 cm) detected on CT (Fig. 1a). A biopsy of the internal mammary lymph node revealed a polyclonal infiltrate of IgG4⁺ plasma cells.
- IgG4-related pachymeningitis in patient 2 presented with progressive headaches, attributed to a meningioma, which was resected. Histology revealed chronic granulomatous inflammation. The diagnosis was only made on review of the biopsy after persistent symptoms from raised intracranial pressure and progressive dural thickening (Fig. 1b) despite empirical treatment for tuberculosis and then neurosarcoidosis (6 months of 25 mg prednisone).
- IgG4⁺ tubulointerstitial nephritis in patient 4 manifested with severe renal failure (eGFR 12 mL/min/1.73 m²) with bilateral renal infiltrates on CT (Fig. 1c). A kidney biopsy confirmed IgG4-RSD.
- IgG4⁺ pulmonary disease in patient 5 manifested with pleuritic chest pain, dyspnoea, fevers and weight loss (20 kg). Positron emission tomography (PET) revealed a 5.8-cm glucose avid lesion in the right upper lobe. Three separate biopsies were interpreted as an inflammatory pseudotumour. The patient subsequently developed bilateral cystoid macular oedema. Suspecting systemic illness, a review of the original lung biopsy revealed IgG4⁺ plasma cell infiltration and lymphoid aggregates in both subpleural lung and pleura.
- An orbital pseudotumour in patient 6 presented with proptosis, erythema, diplopia and radiological evidence of bone infiltration (Fig. 1d).
- Exocrine gland involvement in patient 1 manifested with progressive eyelid and facial swelling from lacrimal and submandibular gland enlargement. She did not have symptoms of glandular insufficiency or obstruction.
- IgG4-related involvement was suspected but not confirmed in two other sites – Patient 6 had multinodular thyroid enlargement on CT with normal thyroid biochemistry, while patient 3 had parotidomegaly.
Table 1 Clinical features and treatment outcomes for six patients with extrapancreatic IgG4-related systemic disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age, ethnicity</th>
<th>Comorbid disease</th>
<th>IgG4 organ involvement</th>
<th>Serum IgG4 at diagnosis (0.06–2.56 g/L)</th>
<th>Histopathology</th>
<th>Time from presentation to IgG4 diagnosis (months)</th>
<th>Treatment</th>
<th>Follow-up duration (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, 51, Vietnamese</td>
<td>—</td>
<td>Lacrimal, sublingual and submandibular gland</td>
<td>5.87</td>
<td>Lacrimal</td>
<td>12</td>
<td>PNL + AZA</td>
<td>72</td>
<td>Remission (two relapses on PNL monotherapy)</td>
</tr>
<tr>
<td>2</td>
<td>F, 72, Croatian</td>
<td>HT</td>
<td>Pachymeningitis</td>
<td>4.83†</td>
<td>Dura</td>
<td>60</td>
<td>PNL + MMF</td>
<td>24</td>
<td>Clinical improvement (stable radiology) Persistent LN</td>
</tr>
<tr>
<td>3</td>
<td>M, 68, Maltese</td>
<td>RA/SjS MGUS</td>
<td>Asymptomatic LN – mediastinal, thoracic, paraspinal Parotid?</td>
<td>13.9</td>
<td>Lymph node</td>
<td>36</td>
<td>PNL + MTX</td>
<td>18</td>
<td>Persistent LN</td>
</tr>
<tr>
<td>4</td>
<td>F, 68, Italian</td>
<td>T2DM</td>
<td>Bilateral diffuse tubulointerstitial nephritis 2 years before: Autoimmune pancreatitis and cholangiopathy LN – mediastinal</td>
<td>4.43</td>
<td>Renal Pancreas</td>
<td>5</td>
<td>MP/PNL + CYP</td>
<td>12</td>
<td>Remission (stable renal failure)</td>
</tr>
<tr>
<td>5</td>
<td>M, 58, white</td>
<td>—</td>
<td>Pulmonary pseudotumour Bilateral cystoid macular oedema</td>
<td>N/A</td>
<td>Lung</td>
<td>15</td>
<td>PNL + MTX</td>
<td>12</td>
<td>Remission</td>
</tr>
<tr>
<td>6</td>
<td>F, 72, Italian</td>
<td>T2DM</td>
<td>Orbital pseudotumour Thyroid?</td>
<td>1.75</td>
<td>Orbital</td>
<td>4</td>
<td>PNL + MMF</td>
<td>10</td>
<td>Remission</td>
</tr>
</tbody>
</table>

†Serum IgG4 for patient 2 was measured on 10 mg prednisone. AZA, azathioprine; CRP, C-reactive protein; CYP, cyclophosphamide; HT, hypertension; ICP, raised intracranial pressure; LN, lymphadenopathy; MGUS, monoclonal gammopathy of uncertain significance; MMF, mycophenolate; MP, methylprednisolone; MTX, methotrexate; PNL, prednisone; RA, rheumatoid arthritis; SjS, Sjögrens; T2DM, type 2 diabetes.
Laboratory features

Histological findings in all biopsies revealed polyclonal IgG4+ plasma cell consistent with IgG4-RSD by criteria (see Methods) (Fig. 2a). Mild eosinophilia was present in two biopsies, while non-caseating granulomas were only seen in the affected dura from patient 2 (Fig. 2b). In addition, scattered admixed mast cells were evident in the renal biopsies of patient 4 (Fig. 2c), while obliterative vascular thrombosis was seen in patient 6 with the orbital pseudotumour.

Serum IgG4 levels were elevated in four of the five patients, with results available prior to combination treatment (patient 4’s level was measured while on 10 mg prednisone). C-reactive protein levels were elevated only in patient 5 (75 mg/L; NR < 10).

Treatment and outcomes

Five of the six patients had symptoms or organ-threatening manifestations sufficient to require treatment with prednisone (mean starting dose 40 mg/day,

Figure 1  (A) Axial computed tomography (CT) demonstrating enlarged paraspinal lymph nodes (blue double arrowhead). (B) Coronal magnetic resonance imaging demonstrating thickened contrast-enhanced meninges over both cerebral hemispheres (red double arrowhead). (C) Axial CT demonstrating diffuse effacement of the kidneys by non-enhancing mass in the kidneys (red arrows) with displacement of normal contrast-enhanced renal parenchyma (blue arrowhead). (D) Axial CT through the orbits with medial soft tissue mass in the right orbital wall with infiltration into the adjacent sinus.
range 25–60 mg) in combination with an additional immunosuppressive drug (Table 1). Azathioprine (AZA; 2 mg/kg/day) was the most common agent chosen. Two patients with AZA-related gastrointestinal intolerance were switched to mycophenolate (MMF; 2 g/day). Methotrexate (MTX; 20 mg/week) was initiated in patient 5 to treat the pulmonary lesion and concurrent cystoid macular oedema. Monthly intravenous cyclophosphamide (0.5 g/m²/month for six cycles) was used to stabilise the severe renal failure in patient 4.

As patient 3 had asymptomatic lymphadenopathy, he was continued on unaltered maintenance treatment for rheumatoid arthritis (prednisone 10 mg/day and MTX 20 mg/week).

In all treated patients, prednisone was gradually tapered by 5 mg/day every 2 weeks to a maintenance dose of 10 mg/day. Treatments with AZA, MMF and MTX were continued over the follow-up period.

Four patients (1, 4, 5, 6) had clinical and radiological remission on combination therapy. Patient 4's renal function stabilised but did not improve. Patient 2 had a partial response, with reported improvement in her headaches despite persistent radiological changes. Patient 3 remained asymptomatic, with stable lymphadenopathy on CT. Post-treatment serum IgG4 levels normalised in two of the three patients with available results.

Relapses only occurred in patient 1 (two separate episodes of salivary gland enlargement), which coincided with non-compliance with AZA.

Treatment was well tolerated. Apart from AZA-related gastrointestinal intolerance, the only other significant adverse effect was prednisone-related hyperglycaemia in the two diabetic patients.

Discussion

IgG4-RSD is a systemic multi-organ infiltrative disease. To date, much of the understanding of this entity is established from the pancreatic involvement of IgG4-RSD, or AIP. However, few reports focus on extra-pancreatic presentation and treatment. This retrospective analysis reviews six patients with histologically confirmed extra-pancreatic IgG4-RSD.

Our cohort's median age at diagnosis was 64 years, which is consistent with other published data. Lymphadenopathy was the most common organ involved in our cohort. Similarly, Hamano et al. reported that lymphadenopathy (80%; hilar region), and salivary and lacrimal gland (39%) involvement were the most common extra-pancreatic findings seen in 64 Japanese patients with established AIP. One patient in our cohort had isolated dural involvement, a rarely reported manifestation of IgG4-RSD. Importantly, only two of the six patients in our cohort had multiple organ involvement with IgG4-RSD. In contrast, a recent report from a French survey of IgG4-RSD patients found that 88% of...
25 patients had involvement of more than one organ. Apart from differences in data collection, these differences also reflect the varied nature of the disease which may remain isolated in a single organ or progress over time to multiple sites.

Clinical manifestations of IgG4-RSD in four of six patients in our cohort occurred without any clinical or radiological pancreatic involvement, consistent with recent data published by Zen and Nakanuma. In this cohort of 114 Japanese patients, isolated extra-pancreatic disease occurred in the lung (14% of cases), salivary and lacrimal glands (20%), and lymph nodes (2%).

The pathogenesis of IgG4-RSD is unknown. Differences in the IgG4 structure from other IgG subclasses render it susceptible to formation of ‘half-antibodies’. Functionally, these half-antibodies may compete and block the inflammatory responses triggered by other antibody iso-types, thus serving a potential immunoregulatory role. It remains unclear, however, if the reason for preferential selection and proliferation of IgG4 plasma cells in IgG4-RSD is a by-product from a chronic immune response to an unidentified antigen, or if IgG4 has a key pathogenic role in the inflammatory reaction.

IgG4-RSD is rare and may mimic the presentation of other diseases. For example, presentations of IgG4-RSD lymphadenopathy may be wrongly considered secondary to tuberculosis, lymphoma or Castleman disease. This can delay diagnosis and result in unnecessary investigations, such as in patient 5, who had repeated lung biopsies for suspected malignancy. Physician awareness of the heterogeneous clinical presentations of IgG4-RSD is, therefore, important.

The diagnosis of IgG4-RSD also relies heavily on accurate and specific immunohistochemistry. While diagnostic criteria for IgG4-RSD are established for pancreatic disease, similar criteria for extra-pancreatic organ involvement, such as the lymph nodes, remain to be firmly established. In addition, a recent study showed that IgG4+ plasma cells may be detected in non-specific chronic inflammatory lesions, such as rheumatoid synovium, localised oral inflammatory lesions or carcinomas. These findings emphasise that an IgG4-RSD diagnosis be made after careful histological interpretation by an experienced histopathologist, and correlation with the clinical manifestations and serum IgG4 levels.

Serum IgG4 is included in the current diagnostic criteria for IgG4-RSD pancreatic disease, with sensitivity approaching 70% and specificity of 90%–95%. Furthermore, serum IgG4 levels may predict extra-pancreatic disease. Kamisawa et al. showed serum IgG4 levels greater than 2.2 g/L, measured by radial immunodiffusion, correlated with extra-pancreatic manifestations. Four of the five patients in our cohort with extra-pancreatic disease had pretreatment levels higher than this level. In addition to diagnosis, serum IgG4 may be a useful marker of disease activity, response to immunosuppression and risk of relapse.

Other investigations may include scintigraphic localisation studies with gallium-67 to identify and monitor sites of active disease. More recently, PET scans have been used to monitor the treatment response in IgG4-RSD. Hence, serum IgG4 and scintigraphy may be useful adjuncts to detect subclinical disease, monitor treatment response and identify early relapse.

Treatment of IgG4-RSD is generally commenced for organ-threatening manifestations.

Corticosteroids are the mainstay of IgG4-RSD treatment, with remission rates approaching 100% in AIP-treated patients. However, relapses after corticosteroid therapy range from 23% to 60%, with reportedly higher rates in patients with extra-pancreatic manifestations. In our cohort, combination treatment with either AZA, MMF or MTX resulted in clinical and radiological remission in four of six patients and stabilised disease in the remaining two patients, consistent with the reported success of these agents when used as second-line treatment. More recently, targeted treatments against antibody production in refractory disease have also been successful with rituximab or bortezomib. In addition to being effective, these immunosuppressants enabled us to minimise corticosteroid-induced hyperglycaemia in two diabetic patients without relapses over the course of follow up.

Conclusion

This analysis highlights the diverse nature of IgG4-RSD presentations in extra-pancreatic manifestations. While our analysis is subject to the inherent deficiencies of retrospective analysis, and possible referral bias to a single centre, we would argue that the spectrum of patients seen is representative of the diverse nature of IgG4-RSD presentations and is consistent with the reported literature. In conclusion, we provide short-term, follow-up data and demonstrate good outcomes with combined immunosuppression in IgG4-RSD. Larger multicentre collaborations are necessary to demonstrate long-term outcomes in this condition.

Acknowledgements

The authors thank Mavis Billinge (Westmead Hospital) for secretarial assistance and the Westmead radiology department for assistance with the images.
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Better estimates of survival for patients considering adjuvant chemotherapy after surgery for early non-small-cell lung cancer

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Key words
non-small-cell lung cancer, prognosis, survival rate, survival estimate.

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Received 1 April 2012; accepted 26 April 2012.

Abstract
Introduction: The aim of this study was to summarise and describe survival data from contemporary randomised trials of platinum-based adjuvant chemotherapy for patients with non-small-cell lung cancer (NSCLC). The goal was to assist clinicians to provide better estimates of survival for patients considering adjuvant chemotherapy following surgical resection for NSCLC.

Methods: Randomised trials of cisplatin-based adjuvant chemotherapy for resected NSCLC were identified. Survival rates at 1, 2, 5, 7 and 10 years and the following percentiles (scenario): 90th (worst case), 75th (lower typical), median, 25th (upper typical) and 10th (best case) were extracted from each overall survival (OS) curve.

Results: Thirty-eight OS curves from 19 trials (7042 patients) were analysed. With adjuvant chemotherapy, the median OS rate (interquartile range) at 1 year was 91% (85–95), 2 years was 73% (69–88), 5 years was 61% (45–65) and 7 years was 49% (38–65). With observation only, the median OS rate (interquartile range) at 1 year was 88% (83–92), 2 years was 74% (65–82), 5 years was 55% (42–58) and 7 years was 40% (34–45). In both arms, survival rates at 2, 5 and 7 years were well estimated by raising the 1-year survival rate to the power of two, five and seven respectively. Few trials reported survival rates at 10 years.

Conclusion: Simple percentages and their powers provide a useful starting point for estimating and describing survival to patients considering adjuvant chemotherapy after surgery for NSCLC.

Introduction
Lung cancer is the leading cause of death from cancer in most Western countries.1 Non-small-cell lung cancer (NSCLC), which accounts for 80% of these cancers, is treated by surgical resection in its early stages, and this remains the foundation of curative treatment. However, despite complete surgical resection, recurrence occurs in 30% to 70% of patients so treated.

Adjuvant chemotherapy aims to reduce the rate of recurrence following surgical resection by eradicating subclinical, micro-metastatic disease. Adjuvant chemotherapy has been evaluated in a series of randomised controlled trials performed over several decades. An updated meta-analysis of individual patient data from 11 137 subjects in trials conducted from 1965 to 2009 demonstrated a hazard ratio for death of 0.86 for adjuvant chemotherapy following surgery that was statistically significant ($P < 0.0001$) and translates into an absolute increase in 5-year survival of 4%, from 60% to 64%.2 This analysis also showed a statistically significant hazard ratio for death of 0.88 ($P = 0.009$) when adjuvant chemotherapy followed surgery and radiotherapy, translating into an absolute increase in 5-year survival of 4%, from 29% to 33%.2

Although these reported hazard ratios and 5-year survival rates accurately summarise the general effects of adjuvant chemotherapy in these groups, these are not particularly helpful to individual patients and do not convey the considerable heterogeneity of individual outcomes that make up these single summary measures. Communicating prognostic information to patients considering adjuvant chemotherapy for resected NSCLC in an understandable and comprehensive format that accurately conveys this heterogeneity and uncertainty remains a challenge for clinicians.

The aim of this study was to help doctors provide better estimates of survival for patients considering adjuvant chemotherapy after surgery for early NSCLC by

Funding: None.
Conflict of interest: None.
providing an approach to describing and summarising survival data from contemporary randomised trials.

**Material and methods**

We searched the Cochrane Central Register of Controlled Trials, MEDLINE and the reference lists of retrieved papers for randomised controlled trials of adjuvant chemotherapy after resection of NSCLC published from January 1965 to July 2010. Key inclusion criteria were: comparison of a platinum-based regimen versus a control arm of observation alone; publication in English and inclusion of Kaplan–Meier curves for overall survival (OS).

We recorded each trial’s year of publication, median follow-up time; numbers and characteristics of participants, tumours, and chemotherapy regimens, and results, including hazard ratios for OS. Each OS curve was digitised and then independently traced by two authors using Un-Scan-It (Silk Scientific, Inc., Orem, UT, USA) to elicit survival rates at 1, 2, 5, 7 and 10 years; median survival and the following percentiles (represented scenario): 90th (worst case), 75th (lower typical), 25th (upper typical) and 10th (best case). These are the percentiles (scenarios) recommended for estimating and discussing prognosis in advanced cancer.\(^3\),\(^4\) Discrepancies between observations were resolved by repeated measurement and discussion.

The 90th percentile (worst-case scenario) is the time by which the 10% of patients doing worst have died. The typical scenario is the range of survival times for the middle 50% of patients (i.e. from the 75th percentile to the 25th percentile). The best-case scenario (10th percentile) is the survival time exceeded by the 10% of patients doing best. These percentiles and scenarios are illustrated in Figure 1. We have previously shown that survival times at these percentiles in trials of chemotherapy for metastatic breast cancer could be predicted reasonably well using the simple multiples of the median: 90th percentile = \(0.25 \times \text{median}\), 75th percentile = \(0.5 \times \text{median}\), 25th percentile = \(2 \times \text{median}\) and 10th percentile = \(3 \times \text{median}\).\(^3\) These multiples are based on the observation that survival curves in advanced cancer are approximately exponential. We hypothesised that this would also be the case for survival curves in trials of adjuvant chemotherapy after curative surgery for NSCLC. This would mean that simple multiples of the median would also provide reasonable estimates of other survival curve percentiles in this context. In addition, if the survival curves were exponential, then survival rates at particular time points could be reasonably estimated by raising the 1-year survival rate to the appropriate power. For example, the survival rates at 2 and 5 years could be estimated by raising the 1-year survival rate to the power of two: (1-year survival rate)\(^2\) and five: (1-year survival rate).\(^3\) We sought to determine the accuracy of these rules of thumb by comparing estimates based on them with values obtained directly from published survival curves.

**Results**

We identified 19 trials, including 38 survival curves and 7042 patients.\(^5\)–\(^24\) The characteristics of the trials are summarised in Table 1. Participants’ characteristics were similar across the trials, with the median percentage of males being 75% (range 62–87%) and median age 61 years (range 56–64). Cisplatin was the platinum agent in 17 trials, while carboplatin was used in two. Tegafur-Uracil was used in five trials. All 38 survival curves provided 1-, 2- and 5-year survival rates; however, not all curves extended beyond 7 years. All 38 survival curves provided a survival time for the 90th percentile (worst case) and 75th percentile (lower typical) values; however, not all trials extended to their median survival.

The median value and interquartile range (IQR) for OS rates at 1, 2, 5, 7 and 10 years are summarised in Table 2.

---

**Figure 1** Example survival curve and relevant percentiles (scenarios). \(\rightarrow\) Observation; \(\rightarrow\rightarrow\) Chemotherapy.

---

\(^3\) The characteristics of the trials are summarised in Table 1. Participants’ characteristics were similar across the trials, with the median percentage of males being 75% (range 62–87%) and median age 61 years (range 56–64). Cisplatin was the platinum agent in 17 trials, while carboplatin was used in two. Tegafur-Uracil was used in five trials. All 38 survival curves provided 1-, 2- and 5-year survival rates; however, not all curves extended beyond 7 years. All 38 survival curves provided a survival time for the 90th percentile (worst case) and 75th percentile (lower typical) values; however, not all trials extended to their median survival.

The median value and interquartile range (IQR) for OS rates at 1, 2, 5, 7 and 10 years are summarised in Table 2.
The medians of the observed survival rates at 2, 5 and 7 years could be predicted reasonably well by raising the median of the observed 1-year survival rates to the appropriate power. For example, raising the median of the observed 1-year survival rates to the power of two provided a reasonable estimate of the median of the observed 2-year survival rates; and raising the median of the observed 1-year survival rates to the power of five provided a reasonable estimate of the median of the observed 5-year survival rates. There were insufficient observations to comment on predictions of 10-year survival rates.

The median value and IQR for survival times at the 90th percentile (worst case), 75th percentile (lower typical), 50th percentile (median) and 25th percentile (upper typical) are summarised in Table 3. Survival times at the 90th percentile and 75th percentiles could be predicted reasonably well using the simple multiples of the median recommended from our previous studies in advanced cancer (0.25 and 0.5 respectively). There were insufficient observations of the 25th and 10th percentiles with which to compare our predictions based on simple multiples.

**Discussion**

OS curves were remarkably consistent across these trials of adjuvant chemotherapy in NSCLC. Survival curves were approximately exponential, and therefore, simple rules of thumb gave useful estimates of OS rates and times. Powers of the 1-year survival rate gave reasonable estimates of survival rates at 2, 5 and 7 years. Multiples of the median survival time gave good estimates of survival times for the worst-case (90th percentile) and lower typical scenarios (75th percentile). These observations

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Trial characteristics</th>
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<tbody>
<tr>
<td>19 trials, 38 survival curves, 7042 patients</td>
<td></td>
</tr>
<tr>
<td>Characteristics</td>
<td>Number [%]</td>
</tr>
<tr>
<td>Year of publication</td>
<td></td>
</tr>
<tr>
<td>1990–1994</td>
<td>4 (21)</td>
</tr>
<tr>
<td>1995–1999</td>
<td>3 (16)</td>
</tr>
<tr>
<td>2000–2004</td>
<td>5 (26)</td>
</tr>
<tr>
<td>2005–2009</td>
<td>4 (21)</td>
</tr>
<tr>
<td>2010</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Number of agents used in treatment arm</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8 (42)</td>
</tr>
<tr>
<td>3</td>
<td>9 (47)</td>
</tr>
<tr>
<td>4</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Platinum agent used</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>17 (89)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Other agents used</td>
<td></td>
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<tr>
<td>Vindesine</td>
<td>9 (47)</td>
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<tr>
<td>Vinorelbine</td>
<td>6 (32)</td>
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<tr>
<td>Tegafur Uracil</td>
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<td>Mitomycin C</td>
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<tr>
<td>Cyclophosphamide</td>
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</tr>
<tr>
<td>Etoposide</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Epleomycin</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Median patients per arm</td>
<td>106 (33–935)</td>
</tr>
<tr>
<td>Median age</td>
<td>61 (54–64)</td>
</tr>
<tr>
<td>Median % males</td>
<td>75 (62–87)</td>
</tr>
<tr>
<td>Percentage squamous cell</td>
<td>44 (15–66)</td>
</tr>
</tbody>
</table>

| Table 2 | Overall survival rates: observed versus predicted by using powers of the median of observed 1-year survival rates |
|---|---|---|---|---|---|
| | 1 year | 2 years | 5 years | 7 years | 10 years |
| Chemotherapy group | | | | | |
| Number of curves | 19 | 19 | 19 | 12 | 4 |
| Observed survival rates: median (IQR) | 91 (85–95) | 73 (69–88) | 61 (45–65) | 49 (38–56) | 49 (42–58) |
| Predicted rates: [1-year survival]² | 87 | 83 | 62 | 52 | 39 |
| Meta-analysis rates, no PORT² | 91 | 82 | 66 | 61 | — |
| Meta-analysis rates, with PORT² | 76 | 56 | 32 | 26 | — |
| Control group | | | | | |
| Number of curves | 19 | 19 | 19 | 11 | 3 |
| Observed survival rates: median (IQR) | 88 (83–92) | 74 (65–82) | 55 (42–58) | 40 (34–45) | 41 (40–48) |
| Predicted rates: [1-year survival]² | 87 | 77 | 53 | 41 | 28 |
| Meta-analysis rates, no PORT² | 91 | 81 | 62 | 56 | — |
| Meta-analysis rates, with PORT² | 73 | 51 | 29 | 24 | — |

Predicted 1-year survival rate shown in italics to signify that it is based on the median of the observed 1-year survival rates. —, insufficient data; IQR, interquartile range; n, number of years; PORT, postoperative radiation therapy.
suggest that these rules of thumb could be useful for clinicians estimating and discussing prognostic information with their patients considering adjuvant chemotherapy following surgery for NSCLC. Patients with early stage cancer want and need prognostic information about their chances of cure, life expectancy and possible side-effects of treatment. However, a large proportion of patients do not understand the terms typically used to explain prognosis, including median survival times and relative risk reductions. A study in 2008 that surveyed newly diagnosed patients with lung cancer showed that although the majority of patients were highly satisfied with their physician’s communication of diagnosis and treatment, only 39% were highly satisfied with their communication about the goals of treatment. In addition, only 58% of patients who were told that the intent of their treatment was curative recalled this fact when surveyed.

Resources are available to help clinicians provide information about the effects of adjuvant chemotherapy on prognosis to their patients with early NSCLC. Adjuvant!Online provides a bar graph of survival rates at 5 years with and without adjuvant chemotherapy. The percentages (including % alive, % dead from cancer and % dead from other causes) are calculated based on the patient’s age, sex, comorbidity and T and N stage. The American Society of Clinical Oncology (ASCO) has also published decision aids for early NSCLC. These provide similar bar graphs of survival at 5 years to Adjuvant!Online based on the patient’s lung cancer stage (IB, II and III). The ASCO decision aid also provides information regarding side-effects of a cisplatin/vinorelbine chemotherapy regimen. These tools are very useful, but they focus on the incremental benefit of chemotherapy and summarise a patient’s future with single-number estimates of their chance of surviving 5 years.

We suggest that clinicians could use these decision aids to estimate an appropriate 5-year survival rate for their patient. Using this 5-year survival rate, clinicians could then apply our simple rules of thumb to elaborate on what these estimates mean to an individual. For example, if Adjuvant!Online estimated a 5-year survival rate of 50%, predicted survival rates at 1, 2 and 7 years would be 87%, 76% and 38% respectively. Other examples are demonstrated in Table 4. Further research should validate the accuracy of estimates based on these simple rules of thumb in other datasets and evaluate their usefulness in the clinic by surveying clinicians and patients.

The recently published meta-analysis of individual updated patient data provide the best evidence about size and nature of survival benefit following adjuvant chemotherapy. Our study complements the meta-analyses by providing a comprehensive summary of the survival data from individual trials using contemporary platinum-based regimens and by providing rules of thumb that can help clinicians describe survival to future patients considering adjuvant chemotherapy following resection of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Overall survival times: observed versus predicted by using simple multiples of the median of the observed survival times</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>90th</td>
</tr>
<tr>
<td></td>
<td>(worst case)</td>
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<tr>
<td>Chemotherapy group</td>
<td></td>
</tr>
<tr>
<td>Number of curves</td>
<td>19</td>
</tr>
<tr>
<td>Observed survival time in months: median (IQR)</td>
<td>13 (9–21)</td>
</tr>
<tr>
<td>Predicted survival time in months</td>
<td>14</td>
</tr>
<tr>
<td>Meta-analysis survival times in months, no PORT</td>
<td>14</td>
</tr>
<tr>
<td>Meta-analysis survival times in months, with PORT</td>
<td>6</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
</tr>
<tr>
<td>Number of curves</td>
<td>19</td>
</tr>
<tr>
<td>Observed survival time in months: median (IQR)</td>
<td>11 (8–13)</td>
</tr>
<tr>
<td>Predicted</td>
<td>11</td>
</tr>
<tr>
<td>Meta-analysis survival times in months, no PORT</td>
<td>13</td>
</tr>
<tr>
<td>Meta-analysis survival times in months, with PORT</td>
<td>6</td>
</tr>
</tbody>
</table>

Predicted median survival time shown in italics to signify that it is based on the median of the observed median survival times. —, insufficient data; IQR, interquartile range; PORT, postoperative radiation therapy.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Examples: using simple rules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated 5-year survival rate (%)</td>
<td>1 year</td>
</tr>
<tr>
<td>70</td>
<td>93</td>
</tr>
<tr>
<td>60</td>
<td>90</td>
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<tr>
<td>50</td>
<td>87</td>
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<tr>
<td>40</td>
<td>83</td>
</tr>
<tr>
<td>30</td>
<td>79</td>
</tr>
</tbody>
</table>
NSCLC. Our study is limited by the use of published summary data rather than individual patient data, and by the lack of survival data beyond 5 years. Longer follow-up data are needed to determine whether our rules of thumb can be used to estimate survival in the longer term.

Participants in randomised trials are not usually typical of patients in routine clinical practice. Estimates of survival rates and times obtained directly from patients in trials will be reasonable for patients with similar characteristics but are likely to be over-optimistic and require downward adjustment for many others. Modest downward adjustments are probably needed both for the baseline survival without chemotherapy and for the incremental benefit of chemotherapy. Population-based studies would be an ideal basis for making adjustments to summary estimates from randomised trials, but such data are lacking. Once a clinician has come up with a suitable estimate of the 5-year survival rate or median survival, our simple rules can be applied to flesh out the implications of these single numbers.

Conclusion

The survival curves from contemporary trials of cisplatin-based chemotherapy were remarkably similar and approximately exponential. Simple rules of thumb gave good estimates of survival rates and times. Clinicians can use this summary and these simple rules to estimate better and describe survival to their patients considering adjuvant chemotherapy after resection of NSCLC.

References


Immunosuppressive properties of mesenchymal stromal cells derived from amnion, placenta, Wharton’s jelly and umbilical cord

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Key words
MSC, immunosuppressive, umbilical cord, Wharton’s jelly, placenta, amnion

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Received 22 November 2011; accepted 23 October 2012.

doi:10.1111/imj.12044

Abstract

Background: The role of bone marrow-derived mesenchymal stromal cells (BM-MSC) in preventing the incidence and ameliorating the severity of graft-versus-host disease (GvHD) has recently been reported. However, as the collection of BM-MSC is an invasive procedure, more accessible sources of MSC are desirable.

Aim: This study aimed to explore the alternative sources of MSC from amnion, placenta, Wharton’s jelly and umbilical cord, which are usually discarded.

Methods: MSC from those tissues were isolated using mechanical dissociation and enzymatic digestion. Their capacity for proliferation and differentiation, and ability to suppress alloreactive T-lymphocytes were studied and compared with those of BM-MSC.

Results: MSC derived from amnion, placenta, Wharton’s jelly and umbilical cord were similar to BM-MSC regarding the cell morphology, the immunophenotype as well as the differentiation ability. These MSC also elicited a similar degree of immunosuppression, as evidenced by the inhibition of alloreactive T-lymphocytes in the mixed lymphocyte reaction, compared with that of BM-MSC. MSC from umbilical cord and Wharton’s jelly had a higher proliferative capacity, whereas those from amnion and placenta had a lower proliferative capacity compared with BM-MSC.

Conclusion: The results obtained from this study suggest that MSC from amnion, placenta, Wharton’s jelly and umbilical cord can therefore be potentially used for substituting BM-MSC in several therapeutic applications, including the treatment of GvHD.

Introduction

Haemopoietic stem cell transplantation (HSCT) is an effective treatment for haematological disorders, including haematological malignancies, aplastic anaemia and thalassaemia. The success of this treatment relies on the elimination of the patient’s bone marrow by high-dose chemotherapy and/or irradiation, and the reconstitution of the haemopoietic system by the donor haemopoietic stem cells. However, donor cells infused also contain mature T cells that can induce graft-versus-host disease (GvHD), a life-threatening complication of allogeneic HSCT.1 These donor T cells are strongly activated by an alloantigen and infiltrate several target organs such as skin, liver, and the gastrointestinal tract, resulting in tissue destruction. T-cell depletion prior to HSCT can reduce the severity of GvHD, but it leads to increased incidence of severe infection, graft rejection2 and relapse of haematological malignancies.3 Thus, a major concern in HSCT is preventing GvHD while minimising the risk of infection.

Funding: This study was supported by the Thailand Research Fund (grant no. RTA 488-0007), the Commission on Higher Education (grant no. CHERES-RG-49), Faculty of Medicine, Thammasat University and Thammasat University.
Conflict of interest: None.

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Mesenchymal stromal cells (MSC) are multipotent cells that have the potential to differentiate into various mesodermal lineages. In addition, the ability to transplant across major histocompatibility complex (MHC) barriers without the need for immune suppression makes MSC an attractive source for cell therapy. A large body of studies have shown that MSC suppress the proliferation of alloreactive T cells, inhibit the differentiation and maturation of dendritic cells, and decrease the production of inflammatory cytokines by immune cells. Because of their immunosuppressive properties, MSC have been used to treat acute refractory GvHD following allogeneic HSCT.

Although bone marrow (BM) represents the main source of MSC for both experimental and clinical studies, the use of BM-derived MSC (BM-MSC) is not always acceptable because of the invasive harvesting procedure. Moreover, the number of BM-MSC has been reported to decline with increasing age. Recent studies have indicated that MSC can be isolated from a variety of tissues, including adipose tissue, umbilical cord, Wharton’s jelly, tissue from amnion, placenta, Wharton’s jelly and umbilical cord represents a promising source of MSC, as it is abundant and easily obtained by non-invasive procedures. The present study aimed to characterise and compare MSC derived from these tissues in term of cell morphology, immunophenotype, proliferation capacity and immunosuppressive properties to those of BM-MSC. Definition of the biological properties of these MSC will help to define the potential for use in clinical applications.

**Methods**

**Isolation and culture of MSC**

This study was approved by the Ethical Committee of the Faculty of Medicine, Thammasat University and Faculty of Medicine Siriraj Hospital, Mahidol University. BM and peripheral blood were obtained from healthy volunteers. Amnion, placenta and umbilical cord were collected after normal deliveries. MSC were isolated and cultured using the methodology previously described. Briefly, mononuclear cells (MNC) from BM were obtained by Ficoll-Hypaque (GE Healthcare, Uppsala, Sweden) density gradient centrifugation and cultured in complete medium (Dulbecco’s Modified Eagle’s Medium (Gibco BRL, Grand Island, NY, USA) containing 2 mM L-glutamine (Gibco BRL) and 10% foetal bovine serum (FBS; BioWhittaker, Walkersville, MD, USA) at a density of $1 \times 10^5$ cells/cm$^2$.

Umbilical cords; Wharton’s jelly, which was obtained after removal of blood vessels from umbilical cord; decidua basalis, which was dissected from the central region of the maternal-facing surface of the placenta, and amnion, which was obtained by mechanically peeling off from chorion, were minced into small pieces and digested with 0.5% trypsin-EDTA (Gibco BRL) for 30 min at 37°C. The cell suspension from each source was cultured in complete medium at 37°C in a humidified atmosphere containing 5% CO$_2$. Culture medium was changed every 3–4 days. The plastic-adherent confluent cells were continuously subcultured and maintained in the complete medium.

**Characterisation of cultured cells**

Primary cultures from BM and postnatal tissues (passages 2–5) were fixed with 1% paraformaldehyde for 15 min and then incubated with fluorescein isothiocyanate or phycoerythrin-conjugated antibodies against CD34 (BD Bioscience, San Jose, CA, USA), CD45 (BD Bioscience), CD73 (BD Bioscience), CD90 (AbD Serotec, Raleigh, NC, USA) and CD105 (AbD Serotec) for 30 min at 4°C. At least 10$^4$ labelled cells were acquired and analysed using FACScalibur with CellQuest software (Becton-Dickinson, San Jose, CA, USA).

**Differentiation potential of cultured MSC**

The differentiation potential of cultured MSC was studied according to the manufacturer’s protocol. For adipogenic differentiation, $8 \times 10^4$ MSC from each source were cultured in NH AdipoDiff Medium (Miltenyi Biotec, Auburn, CA, USA), with complete change of medium every 3 days. After 3 weeks of culture, cells were stained with 0.5% oil red O (Sigma-Aldrich, St Louis, MO, USA) in 60% isopropanol for 20 min at room temperature.

For osteogenic differentiation, $5 \times 10^3$ MSC were cultured in NH OsteoDiff Medium (Miltenyi Biotec), which was replaced twice a week. After 2 weeks of culture, cells were stained for alkaline phosphatase (AP) activity. The controls were cultured in completed medium and carried out in parallel to the experiments.

**Proliferative assay**

In order to access the growth characteristics, $6 \times 10^3$ cultured MSC from postnatal tissues and BM (passages 2–5) were seeded into 24-well plates (Corning, Cambridge, MA, USA). Cells from each well were then harvested on days 2, 4, 6 and 8 for counting by haemocytometer. The mean numbers of cells were
calculated and plotted against culture time to generate a growth curve.

**Mixed lymphocyte reaction assays**

**Labelling responder cells with 5(6)-carboxyfluorescein diacetate N-succinimidyl ester**

MNC from peripheral blood (PB-MNC) of allogeneic healthy volunteers that were obtained after Ficoll-Hypaque density gradient centrifugation were incubated with 0.5 μM 5(6)-carboxyfluorescein diacetate N-succinimidyl ester (CFSE; Sigma-Aldrich, St Louis, MO, USA) for 15 min at 37°C. After washing, the labelled cells were then resuspended in RPMI 1640 medium (Gibco BRL) supplemented with 10% FBS (BioWhittaker) and kept at 4°C.

**Irradiating stimulator cells**

PB-MNC as stimulator cells were irradiated at 3000 rad, resuspended in RPMI 1640 medium supplemented with 10% FBS and stored at room temperature.

**Mixed lymphocyte reaction assay**

CSFE-labelled PB-MNC and irradiated PB-MNC from allogeneic donors were co-cultured at a ratio of 1:1 in a 24-well flat-bottomed plate (Corning) containing MSC derived from postnatal tissues and BM. For the positive control, the mitogen-induced proliferation was performed using 1 × 10⁵ CFSE-labelled PB-MNC cultured with 2 μg/mL phytohaemagglutinin (Sigma) in the absence of MSC. After 5 days of culture, the PB-MNC were harvested and stained with 7-aminoactinomycin D (BD Bioscience) to exclude dead cells. The analysis of cell division was performed using a flow cytometer (FACS-calibur) and CellQuest software. All experiments were performed in triplicate. The data are presented as a proliferative index calculated by the following formula:

\[
\text{Proliferative Index} = \frac{\text{number of cell division (R5)} \times 100}{\text{number of cell division (R5)} + \text{number of cell in original population (R3)}}
\]  

**Statistical analysis**

Data are presented as mean ± standard error of the mean. The analysis of variance test was used to assess the significance of differences between observed data. P-values of less than 0.05 were considered to be statistically significant.

**Results**

**Characteristics of cultured cells**

The cells isolated from postnatal tissues were cultured in the same conditions as the cells isolated from BM. MSC derived from umbilical cords (UC-MSC), Wharton’s jelly (WJ-MSC), placenta (PL-MSC) and amnion (AM-MSC) have spindle-shaped morphology similar to BM-MSC (Fig. 1). UC-MSC, WJ-MSC, PL-MSC and AM-MSC

![Figure 1](image-url)  
*Figure 1* Morphology of mesenchymal stromal cells derived from (a, f) bone marrow, (b, g) umbilical cord, (c, h) Wharton’s jelly, (d, i) placenta and (e, j) amnion. AM-MSC, amnion-derived mesenchymal stromal cells; BM-MSC, bone marrow-derived mesenchymal stromal cells; PL-MSC, placenta-derived mesenchymal stromal cells; WJ-MSC, Wharton’s jelly-derived mesenchymal stromal cells.
could be propagated for 18–22 passages before reaching replicative senescence. In contrast, BM-MSC reached the stage of replicative senescence considerably earlier, at passage 10.

**Immunophenotype of cultured cells**

Immunophenotype of cultured cells was determined by flow cytometry. UC-MSC, WJ-MSC, PL-MSC and AM-MSC exhibited similar immunophenotype as those of BM-MSC, which expressed high levels of MSC markers (CD73, CD90 and CD105) but did not express haemopoietic markers (CD34, CD45) (Fig. 2).

**Differentiation potential of cultured MSC**

Similar to BM-MSC, UC-MSC, WJ-MSC, PL-MSC and AM-MSC gave rise to cells that exhibited the characteristics of adipocytes, that is, large cells with numerous lipid droplets that were positive for oil red O staining (Fig. 3f–j), while the presence of adipocyte-like cells in negative control was not observed (Fig. 3a–e).

For osteogenic differentiation induction, most UC-MSC, WJ-MSC, PL-MSC and AM-MSC exhibited osteoblast characteristics, including intracellular refringent crystals and AP expression, similar to that seen in differentiated BM-MSC (Fig. 3p–t). The negative controls did not express AP activity (Fig. 3k–o).

**Proliferative capacity**

The proliferative assay revealed that UC-MSC and WJ-MSC have greater proliferative capacity than BM-MSC, PL-MSC and AM-MSC. The proliferative capacity of UC-MSC at passages 2 and 3 was similar to that of WJ-MSC (Fig. 4a,b). The proliferative capacity of BM-MSC during the first 4 days was significantly lower than that of UC-MSC and WJ-MSC ($P < 0.05$) (Fig. 4a,b). In contrast, the proliferative capacity of PL-MSC and AM-MSC was significantly lower than that of BM-MSC in all passages examined ($P < 0.05$) (Fig. 4a–d).

**Immunosuppressive capacity**

To determine whether MSC can inhibit the proliferation of alloreactive T-lymphocytes, responder PB-MNC were labelled with CFSE. The gating of cells used to calculate the proliferative index of labelled cells was shown (Fig. 5). UC-MSC, WJ-MSC, PL-MSC, AM-MSC and BM-MSC significantly reduced the proliferation of alloreactive T-lymphocytes compared with control (mixed lymphocyte reaction (MLR) without MSC; $P < 0.05$). In a comparison of the immunosuppressive capacity of MSC from various sources, PL-MSC and AM-MSC displayed a somewhat higher immunosuppressive capacity than BM-MSC, while UC-MSC and WJ-MSC exhibited a somewhat lower immunosuppressive capacity than BM-MSC (Fig. 6). However, the differences in the immunosuppressive capacity among these MSC were not statistically significant ($P > 0.05$).

**Discussion**

Currently, BM-MSC have been used as the main source for various preclinical and clinical applications. However, BM-MSC have several limitations, highlighting the need for alternative sources of MSC for experimental and therapeutic applications. Amnion, placenta, Wharton’s jelly and umbilical cord are composed of mesenchyme; therefore, MSC are considered to be found in these tissues. This study confirmed that amnion, placenta, Wharton’s jelly and umbilical cord can serve as a rich source of MSC, as previously reported. MSC can easily be isolated from these tissues using mechanical and enzymatic digestion. These cells exhibited similar characteristics as those of BM-MSC, including fibroblast-like morphology, immunophenotype and differentiation capacity. They expressed specific mesenchymal markers such as CD73, CD90 and CD105 similar to BM-MSC, and they were negative for haemopoietic markers such as CD34 and CD45, as reported for BM-MSC. AM-MSC, PL-MSC, WJ-MSC and UC-MSC showed signs of differentiation into adipocytes and osteoblasts when incubated in induction medium. The presented data demonstrate that these cells share the minimum criteria for defining MSC according to the International Society for Cellular Therapy. Finally and most importantly, the proliferative capacity of UC-MSC and WJ-MSC was significantly higher than that of BM-MSC, and these cells could be propagated for a longer period in culture. These data are similar to that observed in previous studies. The doubling time of UC-MSC and WJ-MSC is shorter than BM-MSC. In addition, WJ-MSC are able to expand over 300-fold over seven passages with karyotype stability. The higher proliferative capacity is thought to reflect the relatively primitive nature of these MSC compared with adult BM-MSC; however, the mechanisms underlying these differences are presently unknown. Further study of cell-cycle regulation in UC-MSC and WJ-MSC may be beneficial in addressing those questions. Clinical trials of MSC therapy in humans have shown promising results in several clinical settings, including the resolution of corticosteroid-refractory GvHD. Several studies reported that BM-MSC appear to be poorly immunogenic because they express low levels of
Figure 2 Flow cytometric analysis of surface-marker expression on mesenchymal stromal cells (MSC) derived from bone marrow, umbilical cord, Wharton's jelly, placenta and amnion. The grey line shows the profile of negative control. The data shown are representative of those obtained in three different experiments. AM-MSC, amnion-derived mesenchymal stromal cells; BM-MSC, bone marrow-derived mesenchymal stromal cells; PL-MSC, placenta-derived mesenchymal stromal cells; UC-MSC, umbilical cord-derived mesenchymal stromal cells; WJ-MSC, Wharton's jelly-derived mesenchymal stromal cells.
MHC class I molecules and do not express MHC class II molecules. In addition, MSC do not express costimulatory molecules such as CD40, CD80 and CD86 which are involved in the activation of T cells for transplant rejection. Therefore, they could be used as third-party unmatched MSC. BM-MSC also have the potential to induce allograft tolerance; therefore, there is considerable interest in using BM-MSC in HSCT. However, the

Figure 3 Representative photomicrographs of adipogenic and osteogenic differentiation of bone marrow-, umbilical cord-, Wharton's jelly-, placenta- and amnion-derived mesenchymal stromal cells (BM-MSC, UC-MSC, WJ-MSC, PL-MSC and AM-MSC). (f–j) Adipogenic differentiation was evidenced by the formation of lipid droplet (oil red O-positive) in cytoplasm after adipogenic induction using NH AdipoDiff Medium. (a–e) No lipid droplet was observed in the cytoplasm of MSC cultured in completed medium. (p–t) Osteogenic differentiation was evidenced by the formation of alkaline phosphatase-positive aggregates after osteogenic induction using NH OsteoDiff Medium. (k–o) No alkaline phosphatase-positive aggregates were found in cytoplasm of MSC cultured in completed medium.
collection of BM remains an invasive procedure involving significant discomfort to the donor. This study therefore investigated whether AM-MSC, PL-MSC, WJ-MSC and UC-MSC have a similar immunomodulatory capacity as that of BM-MSC. The result supports previous studies on the immunosuppressive properties of BM-MSC, WJ-MSC and BM-MSC in MLR assay. In addition, PL-MSC and AM-MSC exhibited a stronger immunosuppressive effect than that of BM-MSC, at least in terms of the ability to suppress an alloreactive T-lymphocyte in MLR assay. In contrast, UC-MSC and WJ-MSC exhibited a lower immunosuppressive effect than that of BM-MSC. However, these differences in immunosuppressive effect were not significantly different. These findings indicate that these MSC may be useful as alternatives to BM-MSC in the treatment of corticosteroid-refractory acute GvHD. A recent study reported that third-party PL-MSC have been used in a patient with acute myeloid leukaemia without any adverse effects. However, the mechanisms underlying the immunosuppressive effect of these MSC are not well characterised. At present, it is still not apparent whether MSC suppress T-cell proliferation through direct cell–cell contact or through the production of soluble factor(s) such as interleukin-10, leukaemia inhibitory factor, indoleamine oxidase and transforming growth factor-β. The investigation of mechanisms underlying the immunosuppressive effect of these MSC is critical for the use of these MSC in future clinical applications.

One of the most important benefits of obtaining MSC from these tissues is availability. Banking of MSC from these tissues could be established for collection of MSC to be used not only for experimental but also for therapeutic applications. Without the need for human leukocyte antigen matching, MSC from these tissues can be used for multiple patients at numerous clinical settings.
Figure 5. Mixed lymphocyte reaction (MLR) assays were analysed by flow cytometry. (a) Dot plot of forward scatter and side scatter show the T-lymphocyte fraction of peripheral blood mononuclear cells. (b) Dot plot of 5(6)-carboxyfluorescein diacetate N-succinimidyl ester (CFSE) and 7-aminoactinomycin D (7-ADD) show the living T-lymphocytes with CFSE-positive. (c) Dot plot of CFSE and forward scatter show T-lymphocytes labelled with CFSE dividing in response to irradiated peripheral blood-derived mesenchymal stromal cells. UC-MSC, umbilical cord-derived mesenchymal stromal cells; WJ-MSC, Wharton's jelly-derived mesenchymal stromal cells.
Figure 6 Mean value of proliferative index of 5(6)-carboxyfluorescein diacetate N-succinimidyl ester (CFSE)-labelled responder T-lymphocytes (R*) co-cultured with irradiated stimulator T-lymphocytes (Sr) from haploidentical donors and mesenchymal stromal cells (MSC) from various sources. Data are presented as mean ± standard error of the mean (SEM). *P < 0.05: significantly different compared with control (R* + Sr). AM-MSC, amnion-derived mesenchymal stromal cells; BM-MSC, bone marrow-derived mesenchymal stromal cells; PL-MSC, placenta-derived mesenchymal stromal cells; UC-MSC, umbilical cord-derived mesenchymal stromal cells; WJ-MSC, Wharton's jelly-derived mesenchymal stromal cells.

Conclusion

This study demonstrates that amnion, placenta, Wharton’s jelly and umbilical cord represent a rich source of MSC that can be easily isolated and expanded in culture. These MSC display biological properties similar to BM-MSC, suggesting that MSC isolated from such sources may provide non-invasively accessible cellular sources for future clinical applications.

References


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Health behaviours and outcomes associated with fly-in fly-out and shift workers in Western Australia

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Keywords
public health, population surveillance, occupational health.

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Received 9 May 2012; accepted 2 July 2012.

Abstract
Aims: To examine the association of health behaviours and outcomes with employment type in the West Australian adult population.
Methods: Cross-sectional study of employed adults aged 16 years and over using self-reported information collected in the WA Health and Wellbeing Surveillance System between 2008 and 2010. A total of 380 fly-in fly-out (FIFO) workers, 913 shift workers and 10 613 workers of other employment types were identified.
Results: FIFO workers exhibited similar health behaviours to shift workers but had a different sociodemographic profile. Compared with other employment types, FIFO workers were significantly more likely to be current smokers, drink alcohol at risky levels, and be overweight or obese, after adjusting for age, sex and survey sampling strategies. They were less likely to report current mental health problems.
Conclusions: Self-reported health behaviours of FIFO workers differ from other employment types. FIFO workers are expected to increase in number over the next decade, as the mining and resources sector expands in Australia. Our findings suggest that health interventions, whether in the workplace or clinical settings, need to be informed by the demographic mix of the cohort of workers on entry as they are not a homogenous group, and targeted towards specific employment patterns (length of shifts and type of employment) to improve their current and future well-being.

Introduction
The work environment in Australia has changed dramatically over recent years because of globalisation and changing market conditions. As a result, there is greater diversification in the arrangement of working hours with increasing numbers of people employed in non-conventional settings including shift work, which refers to work conducted outside of normal working hours (e.g. 9 am–5 pm), and fly-in fly-out (FIFO) work, which is now a common method for operating mines in Australia.

Western Australia is the largest mining state in Australia with over 545 commercial mining projects and sales worth over $100 billion.¹ It is estimated that over 100 000 people are directly employed in the WA mining industry¹ and approximately 72% of those who work directly in this industry work outside Perth all or some of the time.² The resources boom, and strong mining industry has also led to the emergence of the FIFO work schedule, an arrangement that can involve work for up to 10–12 h per day on a remote mine site for between 1 and 6 weeks at a time. FIFO workers live and work at the mine site for a set period of time then return to their homes in between rosters.

However, there is limited literature examining the impact that FIFO commuting and lifestyle can have on an individual's overall health and well-being. To date, published research has focussed on the impact of this work type on relationships with family, friends and loved ones³–⁵ rather than other health behaviours and outcomes, and none has included a comparison group in their analyses.

Several studies have been undertaken to look at the possible health effects of shift work. These studies have found that shift work can disrupt sleep patterns,⁶ lead to depression and poor mental health,⁷,⁸ and increase the risk of peptic ulcers and cardiovascular disease⁹,¹⁰ as well as type 2 diabetes.¹⁰ This type of employment remains common in Australia with an estimated 1.4 million Australians employed in shift work in 2009.¹¹

Our study aims to document, for the first time, the health behaviours and outcomes associated with different
employment settings in a WA context using data from a population-based health and well-being surveillance system.

Materials and methods

Data collection

The WA Health and Wellbeing Surveillance System (HWSS) is a population-based continuous data collection system that uses computer-assisted telephone interviews to collect information from a random sample of the West Australian population every month. The response rate for the HWSS is consistently above 80%, which provides strong evidence that the estimates produced are reliable and representative of the general population.12

This dataset was used to obtain information on self-reported sociodemographic variables, health behaviours and chronic health outcomes for adult respondents aged 16 years and over, who reported that they were employed, for 2008–2010.

Data collection and reporting were approved by the WA Department of Health Research Ethics Committee.

Variables

Identification of FIFO, shift work or other employment type was derived from several employment questions in the survey. Initially, all individuals confirmed if they were self-employed or employed for wages, salary or payment in-kind. Respondents were then asked if they work FIFO or do some form of work that takes them away from home for a set period each week or month. Respondents who reported working FIFO were then directed to the sociodemographic module. Individuals who did not report working FIFO were further asked if they were a shift worker before completing the sociodemographic module. Persons who identified themselves as employed but not as being employed in FIFO or shift work were classified as ‘other employment types’.

Health behaviour information collected included self-reported smoking status, levels of physical activity during leisure time and work, fruit and vegetable serves usually eaten per day, alcohol consumption, and height and weight measurements. A body mass index (BMI) was derived from these figures by dividing weight (kg) by height (m) squared after adjustment for errors in the self-reported height and weight.13 BMI were classified as not overweight (BMI < 25) or overweight/obese (BMI ≥ 25).

Health outcome information included self-reported chronic health conditions that had ever been diagnosed by a doctor.

Statistical analysis

Data analysis used survey procedure functions in SAS Enterprise Guide version 4.2 (SAS Institute Inc, Cary, NC, USA) that take into account the differential probability of survey selection and permit weighting of the data to provide adjusted standard errors and binomial confidence intervals (CI) and Chi-squared test results. Data were weighted for oversampling of non-metropolitan areas and adjusted to the 2009 age and sex distribution of the estimated resident population for WA.14 This allows extrapolation of the findings to the broader WA population. The responses ‘unsure’ and ‘refused to answer the question’ were excluded from the analysis. These categories and missing values comprised <3% of answers for all variables, except BMI where it made up 7% of all responses, and therefore were unlikely to affect estimates.

Results

Demographics

Based on our sample of 11 906 WA residents and after adjustment for age, sex and sampling strategy, the weighted prevalence estimates indicate that 4.4% (95% CI 3.8–5.0) of the adult, employed population in WA are FIFO workers, 7.4% (95% CI 6.7–8.1) are shift workers and the remaining 88.2% (95% CI 87.3–89.1%) are in other forms of employment.

The ratio of FIFO workers to shift workers was 1:1.7, and the ratio of FIFO workers to other forms of employment was 1:20 for the period 2008–2010.

The social and demographic characteristics differed between the three employment types (Table 1). A higher proportion of FIFO workers was male and aged between 25 and 44 years compared with both shift workers and other employment types.

Shift workers were significantly more likely to be from the most disadvantaged socioeconomic areas and to reside in non-metropolitan areas.

Employment characteristics

FIFO workers were significantly more likely to work in jobs that require heavy labour and/or physically demanding work (25.6%, 95% CI 19.6–31.6%) compared with other employment types (16.5%, 95% CI 15.4–17.5%). However, many FIFO workers still spend most of their work day sitting (36.5%, 95% CI 29.8–43.2%). FIFO workers worked the longest mean hours per day out of the three employment types (11.4 h, FIFO worker; 9.7 h, shift worker; 7.5 h, other employment types).
Health behaviours

Table 2 shows the health behaviours for each group; FIFO and shift workers were generally similar but differed to other employment types. In particular, they were more likely to be current smokers and drink at high-risk levels for long-term harm and short-term harm. In addition, FIFO workers were more likely to be classified as overweight or obese when compared with other employment types.

FIFO workers reported drinking a significantly higher mean number of drinks on a drinking day than other employment types (4.2 drinks compared with 3.4 drinks) and reported a higher mean number of drinking days than both shift workers and other employment types (3 days per week compared with 2 and 2.3 days respectively).

Health outcomes

FIFO workers had a lower self-reported prevalence of current mental health problems compared with shift workers and other employment types. Shift workers were significantly more likely to report having an injury in the past 12 months than other employment types (Table 3).

Discussion

Individuals classified as FIFO workers were significantly more likely than workers in other employment types to engage in risky health behaviours, including smoking and drinking excess levels of alcohol, as well as being more likely to be overweight or obese. Shift workers were similar to FIFO workers with regard to most of their

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**Table 1** Demographic characteristics by employment type

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Fly-in fly-out workers</th>
<th>Shift workers</th>
<th>Other employment types</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>88.5 (83.4–92.6)</td>
<td>65.6 (61.3–69.9)</td>
<td>54.2 (52.8–55.6)</td>
</tr>
<tr>
<td>Female</td>
<td>11.5 (7.4–15.7)</td>
<td>34.4 (30.1–38.7)</td>
<td>45.8 (44.4–47.2)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–44</td>
<td>60.6 [54.0–67.1]</td>
<td>48.3 [43.4–53.1]</td>
<td>46.3 [44.9–47.7]</td>
</tr>
<tr>
<td>45+</td>
<td>35.5 [28.4–40.6]</td>
<td>35.0 [28.4–40.6]</td>
<td>40.4 [39.1–41.6]</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/de facto</td>
<td>72.2 [65.4–79.0]</td>
<td>62.9 [58.2–67.7]</td>
<td>69.7 [68.4–71.0]</td>
</tr>
<tr>
<td>Widowed</td>
<td>N/A</td>
<td>1.4 [0.7–2.0]</td>
<td>1.0 [0.8–1.2]</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>6.4 [3.6–9.2]</td>
<td>7.1 [5.2–8.9]</td>
<td>6.5 [6.0–7.0]</td>
</tr>
<tr>
<td>Never married</td>
<td>20.8 [14.2–27.5]</td>
<td>28.6 [23.9–33.3]</td>
<td>22.8 [21.5–24.1]</td>
</tr>
<tr>
<td>Living arrangement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living with friends</td>
<td>3.3 [0.5–6.1]</td>
<td>4.0 [1.6–6.3]</td>
<td>3.0 [2.4–3.7]</td>
</tr>
<tr>
<td>Living with a partner and children</td>
<td>40.1 [33.1–47.1]</td>
<td>32.7 [28.2–37.1]</td>
<td>37.8 [36.5–39.1]</td>
</tr>
<tr>
<td>Living with a partner but no children</td>
<td>28.8 [22.7–34.8]</td>
<td>28.5 [24.3–32.7]</td>
<td>29.9 [28.7–31.1]</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than year 10</td>
<td>1.9 [0.4–3.4]</td>
<td>1.9 [1.0–2.9]</td>
<td>2.1 [1.8–2.5]</td>
</tr>
<tr>
<td>Year 10 or 11</td>
<td>12.4 [7.6–17.2]</td>
<td>11.3 [8.6–14.0]</td>
<td>13.2 [12.4–14.1]</td>
</tr>
<tr>
<td>Year 12</td>
<td>8.6 [4.9–12.3]</td>
<td>11.9 [8.7–15.1]</td>
<td>13.3 [12.3–14.3]</td>
</tr>
<tr>
<td>Tafe/trade qualification</td>
<td>52.0 [44.9–59.2]</td>
<td>55.0 [50.2–59.8]</td>
<td>42.0 [40.7–43.4]</td>
</tr>
<tr>
<td>Area of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan</td>
<td>80.4 [76.6–84.2]</td>
<td>68.1 [64.6–71.7]</td>
<td>77.4 [76.9–77.9]</td>
</tr>
<tr>
<td>Socioeconomic indexes for areas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1 (most disadvantaged)</td>
<td>9.1 [5.3–12.9]</td>
<td>17.9 [14.1–21.8]</td>
<td>11.2 [10.5–12.0]</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>19.2 [13.5–24.8]</td>
<td>16.7 [13.4–19.9]</td>
<td>17.3 [16.2–18.3]</td>
</tr>
<tr>
<td>Quintile 5 (most advantaged)</td>
<td>25.8 [19.5–32.0]</td>
<td>15.4 [12.1–18.6]</td>
<td>26.1 [24.9–27.3]</td>
</tr>
</tbody>
</table>

CI, confidence interval; N/A, unable to calculate because of numbers <5.
health behaviours but differed in terms of their demographics. In particular, FIFO workers were more likely to be male, reside in the Perth metropolitan region and have a higher socioeconomic status. It is possible that women are less likely to be attracted to a FIFO schedule than shift work in general because of child-bearing or other family responsibilities, as it would keep them away from home for extended periods of time.

FIFO workers were also more likely to be overweight or obese than shift workers. The cross-sectional study design prevents definitive causal inferences being made, but one important distinction between these two groups is that FIFO workers are more likely than shift workers to have the majority of their meals prepared for them. It is also worth noting an additional limitation of the study, namely the self-reported nature of health status that may introduce measurement error, particularly around BMI. To combat this, correction equations were applied to the data to improve the reliability of the estimates.13

FIFO workers had a lower self-reported prevalence of current mental health problems compared with other employment types, a somewhat unexpected finding given the extended periods of isolation from family and friends associated with FIFO work, and medical professional reports of significant relationship and mental health issues.15 At the very least, we need better longitudinal data on this issue and cannot assume that FIFO workers as a group have overall worse mental health. For example, it is at least plausible that our findings may reflect a degree of self-selection by workers to enter this type of employment, where knowledge of the worksite characteristics attracts individuals who are prepared to endure the working conditions, and thus were always more likely to have a lower prevalence of mental health conditions. This ‘healthy hire’ effect has been noted previously in the mining industry in a study by Petsonk et al., which demonstrated that miners had better respiratory function than non-miners despite higher exposure to occupational factors that can impact upon lung health.16

The cross-sectional nature of the analysis precludes further examination of this association.

### Table 2 Health behaviours by employment type

<table>
<thead>
<tr>
<th>Health behaviour</th>
<th>Fly-in fly-out workers % (95% CI)</th>
<th>Shift workers % (95% CI)</th>
<th>Other employment types % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently smokes</td>
<td>26.7 (20.5–33.0)†</td>
<td>25.0 (20.9–29.0)†</td>
<td>17.4 (16.3–18.5)</td>
</tr>
<tr>
<td>Insufficient physical activity</td>
<td>40.4 (33.5–47.4)</td>
<td>49.1 (44.3–53.9)</td>
<td>46.2 (44.8–47.6)</td>
</tr>
<tr>
<td>Insufficient fruit consumption</td>
<td>48.9 (41.7–56.1)</td>
<td>50.6 (45.8–55.5)</td>
<td>47.7 (46.3–49.1)</td>
</tr>
<tr>
<td>Insufficient vegetable consumption</td>
<td>87.7 (82.9–92.5)</td>
<td>89.6 (86.6–92.6)</td>
<td>87.9 (87.1–88.8)</td>
</tr>
<tr>
<td>Consumes more than two alcoholic drinks per day (high risk for long-term harm)</td>
<td>64.7 (57.5–71.9)†</td>
<td>59.0 (53.7–64.3)†</td>
<td>50.9 (49.4–52.4)</td>
</tr>
<tr>
<td>Consumes more than four alcoholic drinks per day (high risk for short-term harm)</td>
<td>29.8 (22.8–36.8)†</td>
<td>30.2 (25.1–35.2)†</td>
<td>21.5 (20.2–22.9)</td>
</tr>
<tr>
<td>Overweight or obese</td>
<td>79.3 (73.2–85.5)†</td>
<td>72.1 (67.5–76.8)</td>
<td>68.0 (66.7–69.4)</td>
</tr>
</tbody>
</table>

†Denotes where prevalence is significantly higher, compared with other employment types using χ² statistic, \( P < 0.01 \). CI, confidence interval.

### Table 3 Prevalence of health outcomes by employment type

<table>
<thead>
<tr>
<th>Health outcomes</th>
<th>Fly-in fly-out workers % (95% CI)</th>
<th>Shift workers % (95% CI)</th>
<th>Other employment types % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>2.3 (0.6–3.9)</td>
<td>2.1 (1.1–3.1)</td>
<td>2.6 (2.2–3.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>N/A (N/A)</td>
<td>0.4 (0.0–0.7)</td>
<td>0.6 (0.4–0.7)</td>
</tr>
<tr>
<td>Current asthma</td>
<td>6.4 (3.0–9.8)</td>
<td>11.9 (8.4–15.3)</td>
<td>8.6 (7.8–9.6)</td>
</tr>
<tr>
<td>Current respiratory condition other than asthma</td>
<td>0.7 (0.1–1.2)</td>
<td>0.7 (0.1–1.3)</td>
<td>1.2 (0.1–1.4)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>10.5 (7.0–14.0)</td>
<td>12.2 (9.5–14.9)</td>
<td>14.4 (13.5–15.2)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.6 (0.1–1.2)</td>
<td>2.1 (1.0–3.2)</td>
<td>2.0 (1.7–2.4)</td>
</tr>
<tr>
<td>Cancer (excluding skin cancer)</td>
<td>1.0 (0.2–1.9)</td>
<td>2.6 (1.0–4.2)</td>
<td>3.1 (2.7–3.5)</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>8.8 (5.5–12.1)</td>
<td>8.2 (5.9–10.5)</td>
<td>8.1 (7.4–8.7)</td>
</tr>
<tr>
<td>Injury in the past 12 months</td>
<td>24.3 (18.2–30.5)</td>
<td>29.9 (25.5–34.3)†</td>
<td>23.3 (22.1–24.5)</td>
</tr>
<tr>
<td>Current mental health problem</td>
<td>7.7 (4.4–11.0)†</td>
<td>13.2 (10.3–16.1)</td>
<td>13.0 (12.1–13.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.1 (0.8–5.3)</td>
<td>3.2 (1.9–4.6)</td>
<td>3.7 (3.3–4.2)</td>
</tr>
</tbody>
</table>

†Denotes where prevalence is significantly higher. §Denotes where prevalence is significantly lower. The symbols indicate that there is a significant difference compared with other employment types using χ², \( P < 0.01 \). CI, confidence interval; N/A, unable to calculate because of numbers <5.
Shift workers were more likely to report an injury in the past 12 months compared with other employment types, although the surveillance system does not distinguish between work-related and other injuries. However, this finding is consistent with a recent ABS survey indicating that 28.1% of people who experienced a work-related injury or illness in Australia in 2009–2010 were working under shift arrangements despite making up only 16% of all employed persons.17

It is probable that the prevalence of FIFO workers and shift workers identified in the population through the surveillance system is an underrepresentation of actual numbers because of the nature of their employment and the need to be contacted on a home phone number between 9 am and 8 pm to complete the survey. Regardless, health surveillance systems are a useful tool to monitor whether these numbers and the ratio between FIFO and shift workers changes in the future.

Billions of dollars of investment is planned for new mining projects and expansions in Western Australia. For example, Chevron’s $50 billion Gorgon project is predicted to employ 10 000 construction workers and 3500 permanent staff by next year, and Rio Tinto will utilise around 8000 FIFOs for its Pilbara expansion.18 The increasing use of FIFO workers in Australia is the subject of a current inquiry by the House of Representatives Standing Committee on Regional Australia. While health is not directly cited in the terms of reference, identifying health profiles for specific employment groups is extremely valuable. Adults spend a significant portion of their day in the workplace so it is imperative to build healthy work environments that will encourage and maintain healthy lifestyle choices.

Conclusion

This study represents the first time that a population-based surveillance system has been used to compare the health profiles of FIFO and other employment types in Australia. It provides important cross-sectional data around their health behaviours and outcomes, without being definitive about the contribution of aspects of the FIFO lifestyle and work patterns to such behaviours and outcomes. Our findings suggest that FIFO workers are not a homogenous group and empirical data are needed to test some of the strongly held opinions about the health effects of FIFO work. Future research should focus on specific aspects of FIFO work, including the length of shifts, the nature of the work (sitting vs manual labour) and patterns of time spent on-site, to inform the development of policies to improve the physical and mental health of FIFO workers.

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BRIEF COMMUNICATION

Lipid profiles and persisting inflammation following critical illness in a Central Australian population: a prospective longitudinal observational study

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Key words
lipid profile, cholesterol, intensive care, infection.

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Received 16 April 2012; accepted 2 August 2012.
doi:10.1111/imj.12086

Abstract
No published data exist following the changes in lipid profile during and after an episode of acute illness for the Australian Indigenous population. This paper presents data focusing on lipid profiles and inflammatory markers in a group of survivors of critical illness in Central Australia, prospectively recruited to a larger trial exploring the medium-term sequelae of an intensive care unit admission. This data confirm that lipid profiles in acute illness are deranged, and that recovery may differ between indigenous and non-indigenous populations.

Altered lipid profiles during critical illness have been recognised for over a decade.1,2 Furthermore, there is a growing body of evidence originating from in vitro experiments and clinical data suggesting that lipoproteins, particularly high-density lipoprotein (HDL), and their associated apolipoproteins are potent modulators of inflammation.3–7

The changes in lipid profiles, although well documented during sepsis, have not been followed beyond the acute illness. Lipid profiles, in particular HDL cholesterol, are known to differ both within the indigenous population8 and within the end-stage renal population,9 both of which are well represented in Central Australia.10,11

To explore this, serial lipid profiles were included in a prospective study examining medium-term sequelae (neurocognitive, functional and quality of life implications) following critical illness in a group of Central Australian patients thought to be at high risk for future morbidity.

It was hypothesised that lipid profiles in a group of Central Australian survivors of critical illness may show a different pattern of recovery to other populations. It was further postulated that this is related to persisting inflammation.

A prospective longitudinal observational study was conducted in the Alice Springs Hospital (ASH) intensive care unit (ICU), a rural medical and surgical ICU. Ethics approval was obtained from the Central Australian Human Research Ethics Committee. Informed consent was obtained prior to discharge from ICU.

Patients admitted to the ASH ICU between February and August 2009, and thought to be at high risk for future morbidity, as defined by profound physiological derangement, were prospectively recruited to the study when predefined eligibility criteria were met. Demographics and ICU admission details were collected, including the primary reason for admission and admitting service (medical or surgical).

Primary end-point was the change in lipid profile (total cholesterol (TC), HDL, low-density lipoprotein (LDL) and triglycerides (TGL)) between ICU admission, hospital discharge and 6 months. Secondary outcomes were markers of inflammation (serial C-reactive protein (CRP)) during the index admission (peak and hospital discharge) and at 6 months, and a single measure of chronic inflammation at 6 months (erythrocyte sedimentation rate (ESR)).
Lipid assays were performed using an enzymatic methodology, and CRP assays were performed by immunoturbidimetric analysis, both on the Ortho-Clinical Diagnostics Vitros Fusion 5.1FS. The ESR assay was performed on the Diesse Vesmatic 10 using a photometric methodology.

Due to the small sample size, median (interquartile range) results are reported. Variables were analysed using appropriate non-parametric tests (Statistica, Statsoft Incorporated, Tulsa, OK, USA).

Given the high proportion of indigenous admissions to the ASH ICU, it was planned a priori to analyse indigenous and non-indigenous subgroups.

The study cohort comprised 18 of a potential 26 patients who met inclusion criteria. All participants had lipid profiles recorded for at least one time point, 13 at two points and 9 recorded at all three time points.

Cohort demographics are presented in Table 1. Of note, 78% of the cohort was indigenous. This subgroup was significantly more likely to be admitted under a medical service ($P = 0.03$) and had a significantly higher Charlson comorbidity index (Table 1). Lipid profiles were available for 13 patients at 6 months; one patient was lost to follow up, and four patients died following hospital discharge. All deaths occurred in the indigenous subgroup.

### Table 1: Cohort demographics and lipid profiles

<table>
<thead>
<tr>
<th></th>
<th>All ($n = 18$)</th>
<th>Indigenous</th>
<th>Non-indigenous</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous</td>
<td>14 (78%)</td>
<td>14</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (72%)</td>
<td>11 (79%)</td>
<td>2 (50%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50 (35–60)</td>
<td>45 (35–57)</td>
<td>61.5 (47–65)</td>
<td>0.37</td>
</tr>
<tr>
<td>Homeless</td>
<td>6 (33%)</td>
<td>6 (43%)</td>
<td>0 (0%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>2 (1–4)</td>
<td>3 (0–6)</td>
<td>0.5 (0–1)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diabetic (type II)</td>
<td>7 (403)</td>
<td>7 (503)</td>
<td>0 (0%)</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI</td>
<td>28 (22–33)</td>
<td>30 (22–34)</td>
<td>28 (21–33)</td>
<td>0.78</td>
</tr>
<tr>
<td>History of alcohol abuse</td>
<td>7 (403)</td>
<td>7 (503)</td>
<td>0 (0%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Smoker</td>
<td>8 (443)</td>
<td>7 (503)</td>
<td>1 (25%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>9 (503)</td>
<td>9 (643)</td>
<td>0 (0%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Emergency admission</td>
<td>18 (100%)</td>
<td>14 (100%)</td>
<td>4 (100%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Medical admitting service</td>
<td>14 (78%)</td>
<td>13 (93%)</td>
<td>1 (25%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Surgical admitting service</td>
<td>4 (22%)</td>
<td>1 (7%)</td>
<td>3 (75%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Median APACHE II</td>
<td>19 (15–23)</td>
<td>19.5 (15–24)</td>
<td>18 (14–20)</td>
<td>0.4</td>
</tr>
<tr>
<td>Ventilated (h)</td>
<td>155 (70–360)</td>
<td>133 (69–360)</td>
<td>181 (140–299)</td>
<td>0.56</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>10 (56%)</td>
<td>8 (57%)</td>
<td>2 (50%)</td>
<td>0.62</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>8 (4–15)</td>
<td>7.5 (3–15)</td>
<td>11 (6–18)</td>
<td>0.71</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>7 (4–12)</td>
<td>6.0 (4–12)</td>
<td>9 (5–21)</td>
<td>0.73</td>
</tr>
<tr>
<td>ICU admission ($n = 12; 3$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>2.9 (2.6–3.9)</td>
<td>2.9 (2.5–3.8)</td>
<td>3.0 (2.7–5.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>0.7 (0.4–1.2)</td>
<td>0.7 (0.5–1.1)</td>
<td>0.4 (0.4–1.3)</td>
<td>0.61</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>1.6 (1.1–2.4)</td>
<td>1.7 (1.2–2.3)</td>
<td>1.1 (0.6–3.1)</td>
<td>0.61</td>
</tr>
<tr>
<td>TGL (mmol/L)</td>
<td>1.6 (0.7–2.7)</td>
<td>1.1 (0.7–2.0)</td>
<td>3.3 (1.6–3.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>CRP peak (mg/L)</td>
<td>253 (119–337)</td>
<td>211 (19–39)</td>
<td>453 (306–582)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital discharge ($n = 10; 4$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>3.6 (2.9–5.0)</td>
<td>3.5 (2.8–4.9)</td>
<td>5.0 (4.0–5.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>0.7 (0.5–1.0)</td>
<td>0.7 (0.4–0.9)</td>
<td>1.0 (0.6–1.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.1 (1.1–3.1)</td>
<td>1.6 (0.9–3.0)</td>
<td>3.2 (2.5–3.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>TGL (mmol/L)</td>
<td>1.7 (1.4–2.2)</td>
<td>1.8 (1.0–2.6)</td>
<td>2.4 (1.2–3.6)</td>
<td>0.93</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>13 (6–58)</td>
<td>11 (6–42)</td>
<td>89 (30–139)</td>
<td>0.17</td>
</tr>
<tr>
<td>6 months ($n = 9; 4$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.5 (3.9–6.1)</td>
<td>4.3 (3.2–5.3)</td>
<td>6.0 (4.7–6.6)</td>
<td>0.22</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>0.9 (0.6–1.5)</td>
<td>0.8 (0.6–0.9)</td>
<td>1.5 (1.3–1.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.8 (1.9–3.5)</td>
<td>2.4 (1.9–2.9)</td>
<td>3.6 (2.2–3.8)</td>
<td>0.40</td>
</tr>
<tr>
<td>TGL (mmol/L)</td>
<td>1.7 (0.8–3.1)</td>
<td>1.7 (0.8–2.6)</td>
<td>2.4 (1.2–3.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>12 (9–19)</td>
<td>13 (10–24)</td>
<td>9 (5–14)</td>
<td>0.24</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>32 (10–46)</td>
<td>35 (32–47)</td>
<td>9 (6–12)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mortality (post-ICU discharge)</td>
<td>4 (22%)</td>
<td>4 (29%)</td>
<td>0 (0%)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Data are presented as absolute value or median with proportion or interquartile range in parenthesis. APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; ICU, intensive care unit; LDL, low-density lipoprotein; LOS, length of stay; TC, total cholesterol; TGL, triglycerides.
Lipid profiles over time are presented in Figure 1. No significant difference was seen at baseline between indigenous and non-indigenous subgroups for any of the four lipid parameters assessed (Table 1). For both indigenous and non-indigenous subgroups, there is a significant increase in TC over the follow-up period (Panel B, $P = 0.03$, $P = 0.05$ respectively). There was an increase in HDL and LDL cholesterol over time within the non-indigenous subgroup that did not reach statistical significance ($P = 0.10$, $P = 0.06$ respectively). The indigenous subgroup did not show any increase in either HDL or LDL cholesterol across the three time points ($P = 0.57$, $P = 0.31$). The recovery in HDL cholesterol within the non-indigenous subgroup and the failure of the indigenous subgroup to recover produce a significant difference between the groups in HDL cholesterol at 6 months (Fig. 1, Panel C), while multivariate analysis of variance (MANOVA) revealed a significant difference between the indigenous and non-indigenous groups for HDL over time ($P = 0.03$). There was no statistically significant difference in lipid levels between the subgroups at any other time points (Table 1), or for MANOVA analyses of TC, LDL and TGL ($P = 0.41$, $P = 0.51$, $P = 0.27$). Separate analyses excluding the three patients missing baseline lipid data did not significantly alter the results (data not shown).

The indigenous subgroup had a significantly lower peak CRP compared with the non-indigenous subgroup (Table 1). CRP levels were not significantly different at hospital discharge or at 6-month follow up. The indigenous subgroup had a significantly higher ESR at 6 months compared with the non-indigenous subgroup (Table 1).

This paper adds further evidence to previous findings of a derangement in lipid profile associated with critical...
illness and provides the first published data extending the follow up time to 6 months. The lipid profiles in this cohort are consistent with other studies in the critically ill.\textsuperscript{1,2,4,6,7,12} HDL and LDL cholesterol levels fall below the population reference range,\textsuperscript{13} and like TC demonstrate recovery during the convalescent period. This paper confirms that recovery continues beyond the acute period. Similar patterns are seen for TC, and the HDL and LDL components. Research examining TGL has produced mixed results,\textsuperscript{14} and this paper supports recent findings that TGL levels remain essentially unchanged.\textsuperscript{2}

However, at the subgroup level, there appear to be differences in recovery between indigenous and non-indigenous subgroups, particularly for HDL (Fig. 1, Panels B–E).

The pathophysiology underlying lipid derangement in critical illness has not been fully elucidated, and it is not obvious whether the alteration in lipid profile is a consequence of physiological derangement or whether lipids have a causative role in organ dysfunction.\textsuperscript{14} But the anti-inflammatory, anti-oxidative, immunomodulatory, platelet-stabilising and endothelial protective properties of lipoproteins, in particular HDL, have been demonstrated in \textit{in vitro} and animal experiments.\textsuperscript{3,4,6,7} This has led to a postulated multifactorial interaction between plasma lipids and inflammation.\textsuperscript{14}

Several possible explanations exist for the differences observed in this study. It may reflect differing disease processes in each subgroup, with indigenous participants more likely to be admitted under a medical service, and having higher rates of comorbid disease. It is possible that a genomic influence exists as previous Australian research has demonstrated a consistently lower HDL level in a ‘well’ indigenous population.\textsuperscript{8} Other explanations include a nutritional deficit, which may support the postulated mechanism behind the observation of an increased mortality seen with ‘improving’ lipid profiles, the so-called phenomenon of reverse epidemiology reported in the end-stage renal failure population\textsuperscript{9} or the presence of a persisting inflammatory state. The significantly higher ESR observed in the indigenous cohort may support the latter possibility; however, several other confounding factors, such as anaemia and renal failure, both of which are endemic in this population, may also contribute and make this association difficult to substantiate.

The significant difference in peak CRP levels between the indigenous and non-indigenous subgroups was a surprising finding, and may be a chance finding due to the small sample size or may represent a real effect. Although acute illness severity (Acute Physiology and Chronic Health Evaluation II score) was similar between the groups, underlying chronic disease (Charlson comorbidity index, higher rates of chronic kidney disease and homelessness) or other genetic differences may result in an altered inflammatory response. Previous studies suggest an inverse relationship between the degree of inflammation and lipid level,\textsuperscript{4,12,14} and a larger sample would be required to delineate this relationship in the indigenous population.

The small numbers of patients recruited clearly limit the conclusions that can be drawn, and these findings need to be further explored in a larger cohort. The differing underlying illness and diagnostic category may have created bias and make it difficult to separate the confounding influences of a primary medical or surgical diagnosis. We did not collect data about the use of cholesterol-lowering medications, which may alter post-hospital discharge lipid profiles.

We believe that this is the first study to prospectively examine lipid profiles following an ICU admission for a critical illness over an extended time period. It adds to the body of evidence that lipid profiles are deranged in critical illness and that recovery is complex, and suggests that it may differ in an indigenous population. Although the underlying mechanism is not clear, it is possible, given the elevated ESR at 6 months, that a persisting inflammatory response may contribute. Larger prospective studies are warranted to clarify this.

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Novel mutation in the TMEM127 gene associated with phaeochromocytoma

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Key words
phaeochromocytoma, TMEM127, epinephrine, adrenal gland neoplasm, genetic disease, paraganglioma.

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Received 2 April 2012; accepted 3 June 2012.

doi:10.1111/imj.12088

A study in 2002 found that up to 24% of patients with apparently sporadic phaeochromocytomas carried an underlying mutation in one of five then-described susceptibility genes: RET proto-oncogene, VHL, SDHB, SDHD and NF1.1 Since then, germline mutations in the SDHC and SDHAF2 genes, and rarely the SDHA, KIF1Bβ and EGLN1 genes, have been reported in kindred with phaeochromocytomas and/or paragangliomas.2-6 In 2010, a new tumour suppressor gene, TMEM127, was identified in phaeochromocytomas,7 and mutations in the MAX gene were identified in 2011.8 To date, 23 patients who carry germline TMEM127 mutations have been identified.9 Both adrenal and extra-adrenal phaeochromocytomas have now been identified in association with germline TMEM127 gene mutations7,10,11 and as yet it is unclear what other pathologies may occur in association with mutations in this gene. The TMEM127 gene,
which is localised to chromosome 2q11.2, carries four exons, and encodes for a highly conserved three-span transmembrane protein that is a negative regulator of mTOR.7 The majority of the mutations described so far are associated with truncation of the protein.10 Herein, we present a patient with a novel mutation in the TMEM127 gene.

A 33-year-old man presented with a 3-year history of palpitations, sweating, headache, anxiety and labile blood pressure.

Biochemical testing confirmed the clinical suspicion of phaeochromocytoma with 24 h urine adrenaline and metadrenaline levels that were elevated tenfold and eightfold, respectively, above the upper limit of the reference range. Urinary noradrenaline and normetanephrine levels were elevated twofold and 2.5-fold, respectively, above the reference range, and the chromogranin A level was elevated at 43 U/L (reference range 0–22). A computed tomography scan demonstrated a 40 × 36 mm right adrenal lesion consistent with a phaeochromocytoma. After blockade, the patient underwent uneventful laparoscopic removal of a right 4-cm phaeochromocytoma. Postoperatively, his plasma-free metanephrines and chromogranin A levels returned to normal.

Six months postoperatively, he developed thyrotoxicosis secondary to Graves’ disease (based on technetium scan and positive thyroid stimulating hormone receptor antibodies), followed by a diagnosis of coeliac disease (endomysial antibody positive and biopsy-proven) 4 months later. There was no family history of phaeochromocytoma; however, his mother reported a history of hypertension diagnosed in her 20s, and she had also been treated with radioactive iodine therapy for Graves’ disease more than a decade earlier.

Given his young age at presentation and despite having no definitive family history of phaeochromocytoma/paraganglioma, genetic testing was advised to determine whether an underlying germline mutation was present. Informed consent for testing was provided after appropriate counselling, and a suite of genes was screened simultaneously for mutations rather than taking a sequential gene approach. Polymerase chain reaction (PCR) and capillary-based Sanger sequencing of leukocyte DNA did not reveal mutations in the RET proto-oncogene (exons 10–16), and the VHL, SDHB, SDHC and SDHD genes (all coding exons). Critically, a novel c.415C>T (p.Gln139X) mutation in exon 3 of the TMEM127 gene (NM_0117849.1) was identified, which would result in a significantly truncated protein. The design of PCR primers for the amplification of coding exons of the above genes used a novel bioinformatic programme incorporating an integrated in silico assessment strategy, together with high throughput amplification.12 Predictive testing of family members was undertaken. The proband’s mother, brother and son tested negative for the mutation. The proband’s 60-year-old father proved to be positive for the c.415C>T (p.Gln139X) mutation, and so is considered at increased risk of developing a phaeochromocytoma, and will require ongoing follow up and screening.

This case demonstrates the importance of testing for germline mutations in patients with sporadic adrenal phaeochromocytomas. Although initial reports suggested that TMEM127 germline mutations were only associated with adrenal phaeochromocytomas,7–10 more recently a report has described that TMEM127 gene mutations may also be associated with extra-adrenal lesions, including head and neck paragangliomas.11 Compared with some of the other familial syndromes, such as VHL in which tumours tend to present at a young age, patients carrying a germline mutation in the TMEM127 gene have a similar age of tumour diagnosis as those who have sporadic lesions (41.5 years vs 45 years).10 The youngest patient so far reported has been 21 years of age,10 and the oldest is 72 years old.10 This information suggests that testing of first-degree relatives of the patient presenting with the phaeochromocytoma for mutations in the TMEM127 gene (predictive testing) should begin in the early teen years to identify mutation carriers who require detailed clinical assessment. Even asymptomatic individuals may harbour a phaeochromocytoma, which may first present as sudden death,13 so screening of mutation carriers for tumours is important, whereas those who test negative for the known mutation do not need ongoing screening and follow up. As such, assessment of germline mutations in the TMEM127 gene should probably be offered to all patients presenting with phaeochromocytoma irrespective of age due to the significant implications for the family members in the event of a positive test.

The penetrance of disease in mutation carriers is not yet known.9 Similarly, it is not yet clear what other pathologies may occur in patients who carry TMEM127 germline mutations, and a clear genotype–phenotype correlation is unlikely to become evident until a larger number of these families is published. While Yao et al. reported no preference of adrenaline or noradrenaline secretion in TMEM127 positive tumours,10 both Neumann et al. and Abermil et al. reported a predominant adrenaline secreting pattern,11–14 which we have also described in the current case. Whether the differential secretion of adrenaline versus noradrenaline will be a useful indicator in prioritising the order of gene testing requires larger numbers to be published. A malignant phaeochromocytoma has been reported in a patient carrying a germline TMEM127 gene mutation.10 In contrast to carriers of SDHB germline mutations who are known to be at high
Results of the recently described immunohistochemical testing for SDHB and SDHA\textsuperscript{16,17} are also helpful to guide the order in which testing could be performed. Once a specific mutation in a susceptibility gene has been identified in an affected family member, then predictive testing of first-degree relatives to assess whether they harbour the mutation is relatively straightforward and inexpensive compared with assessing all genes.

TMEM127 is an important new phaeochromocytoma/paraganglioma susceptibility gene. Patients with a germline TMEM127 gene mutation most often present with an apparently sporadic solitary adrenal phaeochromocytoma. Therefore, genetic testing for germline TMEM127 gene mutations should be considered even if there is low clinical suspicion of a hereditary condition. The priority of testing for a TMEM127 gene mutation compared with other phaeochromocytoma susceptibility genes remains dependent on the clinical, biochemical and immunohistochemical findings.
Immune-mediated cytopenias in human immunodeficiency virus: the first reported case of idiopathic aplastic anaemia successfully treated with immunosuppression

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Key words
HIV, aplastic anaemia, cytopenia.

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Received 4 April 2012; accepted 17 June 2012.
doi:10.1111/imj.12087

Abstract
Although isolated cytopenias are relatively common in human immunodeficiency virus (HIV), the incidence of aplastic anaemia is extremely rare. We report here the first case of a HIV-infected patient who developed severe idiopathic aplastic anaemia, and who was safely and effectively treated with anti-thymocyte globulin and cyclosporin. We briefly review immune-mediated cytopenias in HIV, including their frequency, pathophysiology and management strategies.

The patient was a 48-year-old female with well-controlled human immunodeficiency virus (HIV) diagnosed in 1991. She had no prior AIDS-defining illnesses. She had been adherent to her combination antiretroviral therapy (cART) regimen of emtricitabine 200 mg/tenofovir 300 mg daily, atazanavir 300 mg daily, ritonavir 100 mg daily and raltegravir 400 mg bd. Due to the presence of HIV drug-resistance mutations, her cART was changed to the current regimen 12 months previously. Her only other medications included perindopril and allopurinol for nephrolithiasis in the setting of hyperuricaemia, all of which were started 12 months prior.

The patient was admitted for investigation of pancytopenia noted at regular review. She gave a 9-month history of gradually increasing lethargy and weight loss of 5 kg, and 2 months of regular night sweats. Three months previously, she had an episode of right thoracic herpes zoster treated with valacyclovir. On examination, she displayed no bruising or mouth ulcers. There was no hepatosplenomegaly or palpable lymphadenopathy. Full blood examination revealed a platelet count of $33 \times 10^9/L$, haemoglobin of 94 g/L and white cell count of $5.9 \times 10^9/L$, with neutrophils of $1.86 \times 10^9/L$. The reticulocyte count was 1.1%, with an absolute count of $26.9 \times 10^9/L$.

No dysplasia or blasts were observed on the blood film. Analysis of previous blood counts reveals a progressive fall in haemoglobin, neutrophils and platelets over a 9-month period (Fig. 1), pre-dating her herpes zoster infection. No clonal population was observed on flow cytometry of the peripheral blood, and paroxysmal nocturnal haemoglobinuria was excluded. Vitamin B12 and folate levels were normal, and she was not iron-deficient. Cytomegalovirus (CMV) and parvovirus were negative on polymerase chain reaction (PCR) testing of peripheral blood. PCR testing of blood for Epstein–Barr virus gave a positive result ($3 \times 10^3$ copies/mL), which was not considered significant. CD4 cell count was $1042 \times 10^6/L$, and the HIV load was undetectable (<20 copies/mL). Hepatitis B serology was consistent with past infection (Hepatitis B core Ab positive), with an undetectable DNA viral load. Hepatitis C serology was negative.

Bone marrow biopsy revealed a markedly hypocellular trephine showing reduced to absent trilineage haemopoeisis (Fig. 2). There was no evidence of a malignant infiltrate or an increase in reticulin. Negative PCR test results were obtained for herpes simplex viruses, CMV, Varicella zoster virus (VZV), and human herpes viruses 6 and 8 from the aspirate sample. Cytogenetic analysis was not possible due to the acellular nature of the specimen.

The markedly hypocellular nature of the bone marrow was characteristic of aplastic anaemia (AA), although the blood counts did not fulfil the diagnostic criteria at this
point. Although AA has been described in the setting of primary VZV infection in children, to our knowledge there are no reports post localised reactivation. The decline in blood counts in our patient clearly preceded the episode of thoracic zoster. Allopurinol-induced AA was considered, but this was not supported by the temporal profile of disease onset. A literature review that failed to find an association between any of the antiretroviral drugs and aplasia, coupled with the timing of these therapies and disease onset, suggested that drug-induced aplasia was unlikely. Nevertheless, following the complete cessation of allopurinol, cART was ceased for 2 weeks, during which time the patient’s haematological parameters continued to deteriorate, with count nadirs of 0.36 × 10⁹/L for neutrophils, 7 × 10⁹/L for platelets and 75 g/L for haemoglobin. The ongoing decline in her counts following the cessation of medications supported the diagnosis of idiopathic AA, and treatment for this was instituted. We believe that the AA in this patient with HIV was coincident, rather than a direct consequence of HIV.

As anti-thymocyte globulin (ATG) with cyclosporin is recommended for patients with severe AA older than 40 years, this was chosen as an initial treatment over an allogeneic haemopoietic stem cell transplant. Treatment at standard doses was administered as an inpatient without complication. Her cART regimen was restarted both red cell and platelet support for only 1 week. After this time, no further blood product support was required. Post-treatment, she had no hospital admissions and developed no infectious or non-infectious complications. Ritonavir interfered with cyclosporin dosing in a predictable manner, and the patient achieved therapeutic levels (100–300 mcg/L) on a small dose of cyclosporin 10 mg bd. We performed monthly CD4 cell counts, and HIV and hepatitis B viral loads during and for 3 months post-therapy. Her viral loads remained undetectable, and her CD4 cell count fell to 545 × 10⁶/L (but remained in the normal range) while on cyclosporin. After 4 months, her haematological parameters had markedly improved to a haemoglobin of 141 g/L, a neutrophil count of 2.1 × 10⁹/L and a platelet count of 109 × 10⁹/L. Although the rapid initial count recovery and lack of early requirements for blood products in this case were atypical, she still did not fulfil all criteria for complete response to immunosuppressive therapy as per standard criteria.
AA is defined as pancytopenia in the setting of a hypoplastic marrow with the absence of a malignant infiltrate or excess reticulin. The annual incidence is approximately two per million. The majority of cases are acquired idiopathically. Other causes include drug-induced, post-infectious and inherited forms, but to date HIV is not a recognised cause. In acquired idiopathic cases, an aberrant immune response results in the oligoclonal expansion of cytotoxic T lymphocytes, which destroy haemopoietic progenitor cells, thereby resulting in a markedly hypoplastic/aplastic bone marrow. There are very few reported cases of AA in the setting of HIV. Wolf et al. detailed a 34-year-old HIV-infected man who received an allogeneic haemopoietic stem cell transplant for AA. Shah and Murphy described a HIV-infected child whom they believed developed AA due to HIV infection and who responded to antiretroviral therapy. There are no reported cases in the literature of the use of ATG and cyclosporin for the management of AA in the setting of HIV.

HIV is a retrovirus that infects CD4 positive cells, such as T lymphocytes, monocytes, macrophages, megakaryocytes and haemopoietic progenitor cells. HIV results in a myriad of qualitative and quantitative haematological manifestations, including cytopenias. The first reports of HIV-related cytopenias arose prior to the virus being isolated, and thrombocytopenia was recognised as an early manifestation of AIDS. Thrombocytopenia (defined as a platelet count <50 x 10^9/L) was documented in 8.7% of patients with AIDS and 1.7% of HIV-infected individuals in a study of over 30 000 HIV-positive patients in 1997. More recent data from the Women’s Interagency HIV Study documented neutropenia (<2 x 10^9/L) in 44% of patients, with 7% having counts less than 1 x 10^9/L. In addition, 47% became anaemic during follow up. With the widespread and early use of cART and cyclosporin for the management of AA in the setting of HIV, the frequency of cytopenias is now less.

The presence of cytopenias has consistently been correlated with lower CD4 cell counts and higher HIV viral loads, and associated with poorer overall survival. Furthermore, resolution of cytopenias has been demonstrated with the use of cART and a subsequent rise in CD4 cell counts. Although a direct cytopathic effect may contribute, the principal mechanism by which HIV suppresses haemopoiesis is indirect through cytokine dysregulation. γ-interferon and tumour necrosis factor-α are released by activated lymphocytes in response to HIV infection, and contribute to impaired haemopoiesis. Haemopoietic progenitors express CD4 and critical co-receptors CXCR4 and CCR5 which facilitate HIV cellular entry. Direct in vitro infection of CD34 positive cells with HIV has also been reported.

Additional aberrant immune responses driving cytopenias in HIV infection have been described. Anaemia is the commonest abnormality in HIV-infected patients. HIV directly causes anaemia of chronic disease through cytokine dysregulation and its impact on the bone marrow microenvironment. Neutropenia can also be autoimmune in nature. Mechanisms include the formation of anti-neutrophil antibodies or immune complex attachment and premature neutrophil removal through the reticuloendothelial system. HIV-related thrombocytopenia is thought to be predominantly due to increased immune-mediated platelet destruction. Increased peripheral consumption is due to the non-specific absorption of immune complexes onto the platelet surface, the aberrant production of anti-platelet and anti-HIV antibodies that cross-react with platelet epitopes.

In addition to direct infection of haemopoietic progenitors, secondary causes of cytopenias include opportunistic infection (e.g. Mycobacterium avium complex, parvovirus B19), certain anti-infectives (e.g. trimethoprim-sulphamethoxazole, gancyclovir), nutritional deficiencies, possible lymphomatous infiltration of the marrow and antiretroviral drugs. Zidovudine was associated with significant reductions in haemoglobin when it was used as monotherapy in high doses in the 1980s. Although cytopenias are possible with some nucleoside reverse transcriptase inhibitors, many haematological parameters frequently improve with rising CD4 cell counts and a fall in the viral load. cART represents the first line of treatment in many cases as it will treat HIV and is likely to result in the resolution of the cytopenias. This may be the only therapy required for many patients.

In HIV-related, immune-mediated thrombocytopenia purpura, cART alone may not be adequate, and platelet-directed therapy may be necessary. Treatment options are the same as for the non-HIV population, and include prednisolone, intravenous immunoglobulin (IVIG), antidi and splenectomy. Short-term, high-dose prednisolone (1 mg/kg) has been safely used in the HIV population despite concerns regarding the additional immunosuppression. HIV-associated thrombocytopenia is one of the few approved indications for the use of IVIG. It can result in a platelet count greater than 100 x 10^9/L, although only a minority of patients maintain a count greater than 50 x 10^9/L after cessation. A cross-over study comparing IVIG with anti-D in HIV-associated thrombocytopenia reported a higher platelet count increment and more durable responses with anti-D treatment, although patient numbers were small. Splenectomy has also been proven safe and effective in the HIV population.
This first case report of the use of ATG/cyclosporin for AA in a patient with HIV demonstrates that immunosuppressive therapy can be safe and effective in this setting. Immunosuppression has been successfully used for autoimmune disease (e.g. rheumatoid arthritis, inflammatory bowel disease) in the HIV population. The response to treatment for AA in either a HIV-infected or non-HIV patient depends on the suppression of an aberrant immune response. The additional immunodeficiency that even well-controlled HIV may contribute to this environment is uncertain. We believe that this patient had no significant complications as she started treatment with a high CD4 cell count, and it remained in the immunocompetent range throughout. However, the near-complete response and the absence of complications are interesting considering the complex interplay among potent immunosuppression, cART, neutropenia and qualitative immune system abnormalities in HIV, even within the context of a normal CD4 cell count.

References

Marijuana ‘bong’ smoking and tuberculosis

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Key words
marijuana, bong, pulmonary, TB.

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Received 29 May 2012; accepted 5 August 2012.
doi:10.1111/imj.12089

Abstract
The incidence of tuberculosis in the non-indigenous Australian population is low. However, in this paper we report on three cases of cavitating disease, which seem to be associated with a common illicit drug habit namely smoking marijuana using a makeshift pipe or bong. There was a total of 34 positive contacts of these cases and among the contacts sharing a bong with an index case was associated with a sixfold risk of transmission (odds ratio 6.5, confidence interval 1.4–30.4, \( P = 0.016 \)). When cavitating tuberculosis is detected in a young non-indigenous native born Australian, marijuana use should be considered as a possible risk factor.

While Australia has one of the lowest rates of tuberculosis (TB) in the world, the disease remains a public health problem in the overseas-born and indigenous communities. However, the incidence of TB in the non-indigenous, Australian-born population is low at 0.9 cases per 100 000 compared with 5.7 cases per 100 000 nationally in 2008, according to the National Notifiable Disease Surveillance System.1

Marijuana was the most commonly reported illicit drug used (9.1% of people aged 14 years or older) in the 2007 National Drug Strategy Household Survey.2 We report three cases of pulmonary TB in young Australian-born, non-indigenous adults in the Hunter region where marijuana was possibly a significant factor in the transmission and severity of the disease.

A 26-year-old non-indigenous, Australian-born man (case 1) presented with productive cough, night sweats and weight loss over a couple of months. Investigations revealed multiple cavitating lung lesions in his chest X-ray (CXR) (Fig. 1a), and profuse acid-fast bacilli (AFB) were seen on sputum smear. His human immunodeficiency virus (HIV) test was negative.

He was smoking 15 cigarettes/day and marijuana 10 cones/day through a bong (waterpipe) (Fig. 1b).

Sixty-five contacts were screened. Twenty-six were positive for latent TB infection. One developed active TB. Mantoux tests were defined as positive in patients in contact with an infectious case if there was induration of more than 5 mm in diameter. Most of those positive contacts were from his sporting team who had spent a lot of time together in a changing room. They all denied sharing a bong with the index case.

A 32-year-old non-indigenous, Australian-born woman (case 2) presented with fever, productive cough, weight loss, lethargy and tiredness for 2 months. CXR showed a cavitating lesion, and profuse AFB were seen on sputum smear. Her HIV test was negative.

She was smoking 7 cigarettes/day and marijuana 4–5 cones/day through a bong.

Her sputum culture remained positive for fully sensitive Mycobacterium tuberculosis after 4 months of standard directly observed anti-TB treatment. She continued to smoke marijuana during this time. Fortunately, subsequent cultures became negative.

Twelve contacts were screened. Five were Mantoux positive, four of whom frequently shared a bong with the index case.

A 32-year-old non-indigenous, Australian-born woman (case 3) presented with cavitating lung disease and profuse AFB seen on sputum smear. She had been unwell for a few weeks, with productive cough and fever before admission. Her HIV test was negative.

She was smoking cigarettes 10–30/day and marijuana 3 cones/day through a bong.

Thirty-four contacts were screened and three were Mantoux positive, one of whom shared a bong with her on several occasions.

Genotyping of the cultured mycobacterium for all three cases was performed. The first and second cases are unique and not linked to any previous local clusters. The
third case is linked to a previous local cluster in which sharing marijuana bong smoking may have been a significant risk factor for transmission.3

The three index cases and one contact who developed active TB all completed anti-TB treatment without any major side-effects. They are currently well and deny continued use of a shared bong.

A summary of our contact tracing is shown in Table 1. It was observed that sharing marijuana bong smoking with an active TB case was associated with a statistically significant increased risk of transmission. (odds ratio (OR) 6.5, confidence interval (CI) 1.4–30.4, \( P = 0.016 \)).

All three index cases carry similar characteristics: young age, Australia-born, non-indigenous and regular smoking of marijuana through a bong. They all had severe cavitating pulmonary TB at the time of presentation. In the Hunter region, New South Wales, Australia, there now have been four clusters of young non-indigenous, Australian-born TB cases in which marijuana bong smoking was a common feature. The three reported here, and an earlier cluster reported in 2005.3

Munckhof et al.4 also reported a cluster of pulmonary TB in Australian-born, non-indigenous young adults from North Queensland associated with use of a marijuana waterpipe. It was noted that marijuana waterpipe (bong) smoking was common among cases and contacts, and that sharing marijuana waterpipes was associated with the transmission of TB (OR 2.22, 95% CI 0.96–5.17).

In addition to these Australian reports, Oeltmann et al.5 reported an outbreak of TB in marijuana users in Seattle, USA associated with the practice of ‘hot boxing’ where several users smoke in a confined space.

There are several reasons why marijuana use may contribute to the transmission of TB. Firstly, sharing a ‘bong’, and the practice of ‘hot boxing’ will mimic the overcrowding and breathing ‘second-hand’ air for prolonged periods, which has been historically associated with the disease. In case 1, the index case was a marijuana bong user and probably acquired the disease that way particularly because he had a cavitating CXR appearance on presentation. His contacts all shared a small change room with him, again sharing exhalate for long periods. Secondly, \textit{in vitro} and \textit{in vivo} studies in both experimental animals and human subjects have shown that marijuana smoke will interfere with natural defence mechanisms and immunity.6–12 Marijuana compromises tracheobronchial epithelial function, making mucus clearance less efficient; alveolar macrophages from marijuana smokers have impaired the capacity to phagocyte \textit{Staphylococcus aureus}, and they produce reduced amounts of tumour necrosis factor alpha, granulocyte-macrophage colony-stimulating factor and interleukin-6. These deficiencies could be predicted to enhance susceptibility to mycobacterial infection.

This report has some obvious limitations. It is an observational finding from a small case series in regional New South Wales so it may not be representative. However, there are two other very similar reports from different locations. Also, because marijuana use is illegal, there is certain to be a degree of underreporting.

Nonetheless, given the rarity of severe cavitating TB in this demographic group, and the consistency of the association, we feel that the possibility of marijuana use being a risk factor for TB must be taken seriously, and a formal case control study is required. In the meantime, it would be prudent to enquire about marijuana use in any young

**Table 1** Summary of contact tracing

<table>
<thead>
<tr>
<th>Contacts of case 1</th>
<th>Contacts of case 2</th>
<th>Contacts of case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number screened</td>
<td>65</td>
<td>12</td>
</tr>
<tr>
<td>M+</td>
<td>26‡ (40%)</td>
<td>5 (41%)</td>
</tr>
<tr>
<td>B+, M+</td>
<td>0</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>B+, M−</td>
<td>0</td>
<td>1</td>
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</tbody>
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‡Most were students who attended a lecture at university with the case. Total 111, M+ 34 (30.6%), B+ 7 (20.5%), B+ and M+ 5 (71.4%). Odds ratio 6.5 (confidence interval 1.4–30.4), \( P = 0.016 \). M+, mantoux test positive; M−, mantoux test negative; B+, history of bong sharing present.
person presenting with TB, and in any marijuana smoker presenting with a severe respiratory syndrome, TB should be considered.

Acknowledgements
To our TB patients, to Hunter New England Area Health TB team: CNC Brian Robinson and RN Margaret Worthing, to the Department of General Medicine, Calvary Mater Newcastle, to Public Health Unit Newcastle and to the Department of Respiratory and Sleep Medicine, John Hunter Hospital.

References

LETTERS TO THE EDITOR

Clinical-scientific notes

Refractory long QT syndrome and the role of left cardiac sympathetic denervation

A 43-year-old woman, the proband, experienced syncope at age 9 and was diagnosed with long QT syndrome (LQTS) at age 11 years. Treatment with propranolol 40 mg three times daily (t.d.s.) rendered her asymptomatic. Her husband, three brothers and parents are all unaffected by LQTS. She has four sons; the eldest is asymptomatic; however, the younger three sons are severely symptomatic (Fig. 1).

The second son is 19 years old and has a corrected QT interval (QTc) of 490 ms. Diagnosis of LQTS was made at birth because of neonatal bradycardia and a prolonged QTc interval. Initial treatment was with propranolol 1 mg/kg t.d.s. He remained asymptomatic until the age of 8 years, then presented with dizziness and was found to have episodic sinus bradycardia and torsade de pointes (TdP). An implantable cardioverter-defibrillator (ICD) was implanted, and he remained stable on beta-blocker therapy.

The fourth son is 15 years old and has a QTc interval of 530 ms. He was diagnosed on an electrocardiogram performed at birth and was also treated with propranolol 1 mg/kg t.d.s. He remained asymptomatic until the age of 5 years when he was found unconscious. Cardiac monitoring in hospital demonstrated sinus bradycardia and TdP with a QTc interval of 590 ms. Initial control was achieved with mexiletine and
The third son is 17 years old and has a QTc interval of 510 ms. He was diagnosed with LQTS 2 weeks after birth. After the events of his younger and older brothers, he underwent prophylactic implantation of a single-chamber pacemaker, at another centre, to prevent bradyarrhythmia believed to have triggered TdP in his siblings. However, because of symptomatic TdP (Fig. 2), he was upgraded to an ICD within 1 year. Attempts to change his beta-blocker regimen from propranolol to atenolol resulted in ventricular tachycardia storm. Despite compliance with high-dose propranolol, 160 mg t.d.s., and failure of mexiletine due to ineffectiveness and intolerance, he continued to have a total of six discharges over 1 year from the ICD because of increasingly frequent episodes of TdP and ventricular fibrillation (VF). Genetic testing revealed the LQT2 genotype caused by a missense mutation in exon 8 of the KCNH2 gene. This mutation, which results in the substitution of valine for alanine, has been previously identified in affected LQTS patients, and functional studies have demonstrated a resultant trafficking defect.1

A multidisciplinary team consisting of a panel of cardiac electrophysiologists and vascular surgeons reviewed the case, and a thoracoscopically guided left cardiac sympathetic denervation (LCSD) was undertaken to achieve arrhythmia control. Postoperative recovery has been uncomplicated, and no further ICD discharges were noted after 6 months follow up. There have been no episodes of ventricular tachycardia logged on the ICD despite the patient resuming activities, such as sport and farm work, that would have previously precipitated an event. LQTS is a genetic channelopathy, with variable penetrance,7 characterised by abnormally prolonged cardiac repolarisation leading to life-threatening arrhythmias in the presence of a structurally normal heart. It was first described in 1957 when the constellation of congenital deafness, QT interval prolongation, syncope and sudden death were noted among several children in one family. This later became known as the Jervell and Lange-Nielsen syndrome, which results from homozygous or compound heterozygous mutations in the KCNQ1 and KCNE1 genes.3 Currently 13 genetic subtypes (LQT1–13) have been described, of which LQT1, 2 and 3 account for greater than 90% of all cases. These genetic mutations cause ventricular arrhythmias by altering the structure and function of transmembrane ion channels and the regulatory proteins involved in cardiac repolarisation.4 TdP is the characteristic arrhythmia and is thought to be potentiated by triggered activity from adrenergic stimulation. Hence, anti-adrenergic interventions form the cornerstone of therapy. Beta-blockers are first-line medical therapy; however, their efficacy is variable among the different genetic subtypes. In LQT1 beta-blockers are highly effective with 90% of patients free from syncope and cardiac arrest after 5 years follow up, with a total mortality rate of 1%.5 In LQT2 beta-blockers are less effective with a decrease in cardiac events from 58% to 23% after the same follow-up period.6 In contrast patients with LQT3 show no evidence of a reduction in cardiac event rates when treated with beta-blockers.6

The second anti-adrenergic intervention available for the management of LQTS is LCSD, a surgical procedure that pre-dates the beta-blocker era. It is indicated in those who continue to experience syncope or cardiac arrest despite beta-blockade.7 First performed in 19708 it involves the resection of the left sympathetic trunk from the lower half of the stellate ganglion to the level of T4, thereby interrupting the cardiac sympathetic contribution through the cervical and thoracic cardiac nerves. More recently this procedure can be achieved using

Figure 1 Pedigree of family with long QT syndrome. Three out of four brothers are affected as is their mother, the proband. The third son who had the left cardiac sympathetic denervation (LCSD) is shown by the arrow. The proband’s siblings, parents and husband are unaffected. LQTS.
minimally invasive techniques. The main procedural complications to take into account include pneumothorax and Horner syndrome. A variety of mechanisms of action for the procedure has been proposed, including lengthening of ventricular refractoriness, raising the VF threshold and shortening the QTc duration resulting in electrical remodelling. The largest analysis of the efficacy of LCSD demonstrated a significant reduction in the frequency and occurrence of both syncope and cardiac arrest. In those with an ICD who had the procedure performed because of frequent shocks, it reduced the median number of shocks per patient from 25 to 0.

The use of ICD is indicated, in addition to beta-blockers, for both secondary (postcardiac arrest or aborted sudden death) and primary prevention in high-risk patients. However, a variety of specific device-related issues needs to be taken into account before implantation, particularly in growing children, such as lead fracture, inappropriate therapy, venocclusion, age, weight and future growth. Cost-effectiveness analysis comparing non-ICD with ICD therapy in LQTS patients (age range 10–75 years) demonstrated that primary ICD therapy is cost-effective in high-risk males and cost-saving in high-risk females.

In conclusion LCSD should be considered as a treatment option in patients with LQTS who continue to have cardiac events on a maximally tolerated dose of beta-blocker therapy. It may also be an option for patients with asthma or who are unable to tolerate beta-blocker therapy. However, a variety of procedural considerations needs to be taken into account prior to subjecting patients to this invasive option. Careful preoperative and intraoperative medical optimisation and an experienced surgeon are paramount to provide good long-term results while minimising complications.

Received 24 April 2012; accepted 22 May 2012.
doi:10.1111/imj.12090

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Figure 2 Electrocardiogram (ECG) during a typical episode of torsade de pointes (TdP). The first and second sinus beats are followed by two early after depolarisations (EAD). The third sinus beat is followed by one EAD, which initiates the TdP.
Systemic mastocytosis associated with severe osteoporosis in a male patient

A 42-year-old man presented with low back pain for 2 months and pathological spinal fractures. He had experienced generalised flushing episodes associated with diarrhoea for 3 years, diagnosed as presumed carcinoid syndrome. He also reported a past adverse reaction to an iodinated contrast agent.

Physical examination revealed hyperpigmented macules over the lower extremities. The laboratory assessment, including cortisol, free testosterone, intact parathyroid hormone, 25-hydroxy vitamin D, 1,25-dihydroxy-vitamin D, thyroid-stimulating hormone, tumour markers, serum immunofixation electrophoresis test, serum and urinary catecholamines, and 5-hydroxyindoleacetic acid, were unremarkable. Spinal X-rays and magnetic resonance imaging revealed generalised osteopenia, scattered lytic lesions and L2–L5 fractures, vitamin D, zoledronic acid and teriparatide. Additionally, a vertebroplasty at L4 and L5 was performed.

A vertebral biopsy was performed, revealing hypercellular bone marrow. There were irregular cell infiltrates of spindle-shaped mast cells (MC) with granulated cytoplasm, located at paratrabecular sites (Fig. 1B,C). A bone marrow aspirate revealed normocellular bone marrow with 2% pathological MC. The immunophenotype of MC was aberrant with expression of: CD45++, CD117+++, CD34−, CD25++, FceRI++. A mutation of c-KIT (D816V, A7176-T) was detected in MC.

The total serum tryptase level was 344 mcg/L (N: 0–200). A 24-h urine test showed hypercalciuria of 13.98 mmol/day (N: 1.25–6.5), urinary histamine of 0.54 mmol/day (N: 0–0.49) and N-methyl imidazole acid of 0.05 mmol/day (N: 0–0.05).

Based on the presence of one major and four minor criteria according to the World Health Organization definition, a diagnosis of systemic mastocytosis was made. In the absence of haematological abnormalities, hepatosplenomegaly and tissue dysfunction, the patient achieved diagnostic criteria of indolent systemic mastocytosis (ISM), osseous subvariant. He was treated with tramadol, ranitidine, antihistamines, calcium supplements, vitamin D, zoledronic acid and teriparatide. Additionally, a vertebroplasty at L4 and L5 was performed.

Systemic mastocytosis is a rare disease. Its pathogenesis is not well understood, although mutations that activate c-KIT play a fundamental role. Typical symptoms include flushing, abdominal and osseous pain, diarrhoea, unexplained syncope and urticaria pigmentosa lesions.

In ISM, the symptoms and signs of the disease are usually related to the release of MC mediators and, to a lesser extent, to the tissue MC burden. The effects of histamine acting through H1 and H2 receptors include vasodilatation and vascular permeability, explaining the...
patient’s flushing and hypotension. The precipitating factors for MC degranulation include general anaesthetics, radiographic contrast studies, aspirin, non-steroidal anti-inflammatory drugs, opiates and bee stings. Our patient’s previous adverse reaction to iodinated contrast may be relevant in this context.

Osteoporosis results from MC infiltrates in bone marrow and release of MC mediators (essentially histamine and interleukin-6), activating osteoclasts and mediating bone loss. Bone densitometry should be assessed in these patients. Osteoporosis and pathological fractures are found in 28% and 37% of the patients with ISM respectively.

Elevated serum tryptase concentrations should be used as a screening test. In ISM, treatment is essentially symptomatic, based on antihistamines and MC modulators. Avoidance of triggering factors is a major component of the treatment. Bisphosphonates are effective in patients with osteoporotic ISM. Severe osteoporosis might benefit from interferon-alpha therapy. Life expectancy in ISM is not different from the general population.

Our case highlights that systemic mastocytosis should be included in the differential diagnosis of severe, unexplained osteoporosis and that bone biopsy may assist in achieving a specific diagnosis.

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Haemophagocytic lymphohistiocytosis and primary central nervous system lymphoma

A 27-year-old white woman presented with fevers, night sweats and significant weight loss. She was worked-up for fever of unknown origin, in the context of her employment as veterinary technologist and her recent travel to the Caribbean, but it failed to reveal an infectious aetiology. She had no skin manifestations or neurologic deficit or symptoms. She had normocytic normochromic anaemia (haemoglobin of 7 g/dL) and mild thrombocytopenia (110–150 × 10^9/L), and had reactive bone marrow morphology. Early laboratory studies revealed serum sodium of 129–131 mEq/L, total bilirubin of 1.1 mg/dL, serum albumin of 1.6 g/dL and gradually rising liver enzymes, with alanine aminotransferase/aspartate aminotransferase reaching a peak value of 260/88 IU/L (normal range of 8–34 IU/L). Erythrocyte sedimentation rate was 140 mm/h. An extensive infectious disease work-up ruled out Lyme disease, babesiosis, malaria, chikungunya, dengue, histoplasmosis, blastomycoses, coccidioidomycosis, brucellosis, leptospirosis and bartonellosis. The following viruses were tested for by serology, and there was no evidence of active viral infection: Epstein–Barr virus, cytomegalovirus, HIV and hepatitis (A, B and C). Parvovirus immunoglobulin G was positive, but polymerase chain reaction for parvovirus DNA was negative. Serology was also negative for connective tissue diseases: antinuclear antibody, antitissue plasmin antibody, anti-SS-A and SS-B, and antineutrophil cytoplasmic antibody. Imaging studies showed marked splenomegaly (22.9 cm). A whole-body positron emission tomography-computed tomography (PET-CT) scan detected increased uptake diffusely in the spleen with a standardised uptake value (SU V) of 3.5 and an isolated hypermetabolic focus of the left adrenal with a SU Vmax of 11. Fine-needle aspiration of the left adrenal demonstrating the presence of atypical lymphoid cells was suggestive of B-cell lymphoma. A CT-guided core biopsy of the adrenal gland, however, was unable to confirm the diagnosis of lymphoma. She underwent splenectomy, which revealed extensive haemophagocytosis of all blood elements in the red pulp. A repeat bone marrow examination demonstrated normocellular marrow with mature trilineage haemopoiesis and mild haemophagocytosis. A diagnosis of haemophagocytic lymphohistiocytosis (HLH) was supported by hyperferritinaemia (5170 mg/dL) and markedly elevated soluble CD25 (soluble interleukin-2 receptor (sIL-2R)) in serum. However, serum fibrinogen was elevated (848 mg/dL) and natural killer (NK)-cell function was reportedly normal. In addition, PRF1 and UNC13-D gene analysis was negative for the respective mutations.

HLH is a rare disease and is thought to be due to immune dysregulation with overactivation of macrophages and diminished cytotoxic T-cell and NK-cell function.1–2 If untreated, it is uniformly fatal and is associated with a median survival of less than 2 months. The criteria for a diagnosis of HLH include five of the following eight findings: (i) fever, (ii) splenomegaly, (iii) cytopenias (at least two of three lineages), (iv) hypertriglyceridaemia and/or hypofibrinogenaemia, (v) haemophagocytosis in bone marrow, spleen or lymph nodes, (vi) low or absent NK-cell activity, (vii) hyperferritinaemia, and (viii) high levels of sIL-2R. HLH can be divided into two subgroups, primary (familial; FHL) or secondary (acquired). In FHL, a subset of patients has been described with mutations in the PRF1, UNC13-D or STX11 genes. The definitive treatment of primary HLH, with curative potential, is allogeneic transplantation.3,4 Secondary HLH can occur with malignancy, infection or autoimmune/ inflammatory disorders. Malignancy-associated HLH has been most commonly reported in the setting of T-cell or NK-cell leukemias and lymphomas, while reports of HLH with B-cell malignancies are rare. Presumably, malignant cells secrete pro-inflammatory cytokines such as tumour necrosis factor-α and IL-6 that contribute to immune dysregulation.

Initially, the prevailing notion was that HLH was secondary to another process, such as lymphoma, after infectious aetiology had been eliminated. Therefore, a confirmation of the suspicion of lymphoma was attempted by another PET-CT about 3 weeks after the first one. On the contrary, it showed that the adrenal gland was no longer fluorodeoxyglucose (FDG) avid. Hence, she was presumptively diagnosed with primary (familial) HLH. She was started on immunosuppressive therapy, but not before she had developed complications including acute renal failure and hypoxic respiratory failure, requiring mechanical ventilation. The global picture was likely explained by infiltrative processes in the kidneys and lungs from the haemophagocytic syndrome. The HLH was treated to remission with 8 weeks of combination regimen of steroids (dexamethasone taper) and weekly etoposide (VP-16; 150 mg/m² IV), followed by maintenance tacrolimus (1 mg per os two times daily). This therapy was based on the HLH-2004 study protocol.5 With treatment, over time, her renal and respiratory functions recovered. There have been reports of short-term benefit with the use of intravenous immunoglobulin for HLH.6,3 However, it was not used for our patient.

About 3 months after the initiation of therapy, she presented with generalised tonic-clonic seizures (GTCS).
A magnetic resonance imaging (MRI) brain showed vasogenic oedema in the right posterior frontal lobe, left parietotemporal lobe, surrounding two small (10- and 6-mm) lesions. There was also a smaller area of oedema in the right occipital lobe. She then underwent biopsy of one of the brain lesions, which confirmed the diagnosis of large B-cell lymphoma. Interestingly, she had not had any imaging of the head at the time of her first presentation, and the whole-body PET-CT scans done then did not image the brain. It is possible that the lymphoma may have been already present at that time, but was otherwise asymptomatic. Zhang et al. investigated the role of FDG-PET in the differential diagnosis of secondary HLH (sHLH). They reported on 18 patients with sHLH and showed that SUVmax of patients in malignancy-associated HLH group was significantly higher than those of patients with infection-associated HLH (mean 12.0 vs 6.8, \( P = 0.015 \)) and autoimmune HLH (mean 12.0 vs 2.7, \( P = 0.045 \)). However, no significant difference in survival was found among the three subtypes \( (P > 0.05) \).

With the discovery of the primary central nervous system lymphoma (PCNSL), the HLH was now labelled secondary or lymphoma-associated HLH syndrome. The lymphoma treatment was based on high-dose methotrexate and high-dose cytarabine. It was administered for six cycles. The regimen was adapted from a German multicentre prospective study published in 2003. This phase II trial involved treatment of 65 adult patients with B-cell PCNSL. It reported an objective response rate of 71%. The median time to treatment failure was 21 months and median overall survival was 50 months.

A month after completing the chemotherapy, GTCS recurred. MRI of the brain showed moderately increased right frontal vasogenic oedema with subacute haemorrhage in the prior right frontal operative bed, but no definite enhancement. Whole-brain radiation therapy immediately followed. Clinical follow up over 24 months since therapy has been uneventful, without any sign/symptom indicating relapse of lymphoma or HLH.

In summary, this rare case of lymphoma-associated HLH preceded the diagnosis of PCNSL. The lymphoma treatment led to remission not only of the lymphoma, but also kept the HLH in remission. This case illustrates that HLH can be a challenge to diagnose and that evaluation for the primary process is important for deciding the right treatment and determining the prognosis. In this case, once the diagnosis of PCNSL was established, the therapeutic strategy for HLH was appropriately redirected to definitive lymphoma therapy.

Received 15 September 2012; accepted 23 December 2012.

doi:10.1111/imj.12093

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In their review article into the prevalence of gout and hyperuricaemia in Australia,1 Robinson and his co-authors note that gout in Australian Aborigines was not reported until 2000.2 Prior to that date, gouty arthritis appeared to be absent in Australian Aborigines.

In Western Europe and the USA, gout is now the most common form of inflammatory arthritis in males.3 All the known risk factors for gout are now more common in the general as well as the Australian Aborigine populations, i.e. obesity, hypertension, hyperlipidaemia, hyperglycaemia and chronic kidney disease (CKD).3

A recent publication suggests that gout is an independent risk factor for CKD.4 Given the high prevalence of CKD and other chronic diseases in Australian Aborigines, it is imperative to address hyperuricaemia with a focus on prevention and effective treatment.

In 1965, I was a member of a research team comprising a cardiologist, Dr D. Galbraith, a virologist, Professor R. L. Doherty, and a rheumatologist (author). We went to two Aboriginal missions on the Cape York Peninsula at Aurukun and Weipa. Dr Galbraith was investigating rheumatic heart disease in children, Dr Doherty collected blood principally for viral studies and I undertook clinical examination of adults over the age of 20, looking for evidence of rheumatic disorders.5 This work also contributed to Professor Emmerson’s early studies of gout.6

In the Cape York study, I examined 288 adult Aborigines for rheumatic disorders: 217 at Aurukun Aboriginal mission and 71 at Weipa mission. I found no clinical evidence of gouty arthritis in these populations. This was supported by the response to enquiries in 1967 to various missions and flying doctor bases around Australia, indicating that no cases of gout in full-blood Aboriginals had come to their notice. The significance of these observations is that, unlike Polynesian and Maori peoples, Australian Aboriginals do not appear to be inherently predisposed to gout.

In relation to the risk factors for gout, in the 1960s Aboriginal missions did not allow alcohol, and at Aurukun they were encouraged to continue with traditional hunting practices. With the assistance of the mission nursing sister in Aurukun height, weight and blood pressure were also recorded. Measurements were made in 134 females and 81 males. Overweight was recorded in only one 53-year-old woman whose body mass index was 26 kg/m2.7 There was little hypertension recorded.

It is clear that since 1965, significant changes in environment and lifestyle have led to an increase in risk factors for gout. In fact, gout can be regarded as a marker for the presence of other metabolic disorders. Therefore, gout is an important condition and should be a priority for epidemiological and clinical research that will benefit all Australians. I support Robinson’s call for new research into this problem.

Acknowledgement

My role in the 1965 Cape York study was funded by the Australian Arthritis and Rheumatism Council (now Arthritis Australia).

Received 4 December 2012; accepted 30 December 2012.

doi:10.1111/imj.12107

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References

Author reply

We thank Douglas for his comment on our article and on the new information he has provided on the health of those Australian Aborigines he examined in 1965.1,2 It would seem from more contemporary reports of the general health of Australian Aborigines that the prevalence of hypertension and overweight has increased compared with the figures that Douglas reports from 1965.3 The report suggests that in the absence of 21st-century environmental risk factors for gout, such as alcohol and sugar-sweetened beverage consumption, Australian Aborigines historically had a very low rate of gouty arthritis. There is a small amount of published work on gout in Australian Aborigines, including a recent report on gout occurring in inpatients in the Townsville Hospital in North Queensland from 2001 to 2010. Aborigines and Torres Strait Islanders made up disproportionately more (23%) of the gout group compared with only 12% of the control group.4 This suggests that in the presence of 21st-century environmental risk factors, gout prevalence is appreciable in Australian Aborigines, in contrast to the absence reported in 1965. This influence on gout of the westernised environment would be analogous to the situation in the Polynesian Tokelau people, for example, who had low levels of gout reported in their island environment, but on migration to metropolitan New Zealand, their gout prevalence rose substantially.5 There is little doubt that diet and environmental influences, as well as admixture with European populations, will have substantially changed the epidemiology of gout in contemporary Australian Aborigines. Very little is known about the inherited and environmental causes of gout in Australian Aborigines, in comparison with other Australasian populations.6 Given that findings from other populations are highly unlikely to be transferable to Australian Aborigines owing both to unique environmental exposures, social conditions7 and genetic history (with a split from Eurasians 62 000–75 000 years before present, before European and East Asian split8), we agree that priority should be given to further research on the causes and natural history of gout in Australian Aborigines. This is especially important given the association of gout with other chronic metabolic disease.

Received 28 January 2013; accepted 5 February 2013.
doi:10.1111/imj.12094

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Challenges in performing surveillance for central line associated bacteraemia in haematology-oncology units

We note Dix and colleagues’ recent article on monitoring the complications of central venous catheterisation, including rates of central line-associated bloodstream infection (CLABSI) in haematology patients.1 Consistent with study findings, rates of CLABSI in Australian haematology patients have previously been reported as 7.5/1000 central venous catheter days.2 We have performed surveillance for CLABSI throughout our hospital, including haematology patients, for several years, and wish to highlight the challenges in conducting standardised surveillance and in interpreting infection rates in this population.
Many centres use the National Healthcare Safety Network (NHSN) definition for CLABSI monitoring, which was originally developed for mixed intensive care unit (ICU) populations.1 CLABSI is defined as a bloodstream infection with a recognised pathogen that cannot be ascribed definitively to another site or repeated isolation of a common commensal organism together with signs consistent with infection.1 In patients with haematological malignancy, several problems arise when this definition is applied.

First, the definition does not acknowledge mucositis because of chemotherapy, radiation or graft versus host disease as a primary source of bloodstream infection, despite the fact that translocation of enteric organisms is clinically accepted as a cause of bacteraemia. Similar problems arise with other deep sources of infection where a clinical diagnosis is evident, but confirmatory investigations may not be able to be performed (e.g. typhlitis). Second, the current surveillance definition for CLABSI classifies Enterococci species as pathogens, despite these being potential contaminants, especially when detected in a single blood culture.4 Third, the definition of bloodstream infection does not distinguish blood cultures taken through peripheral venipuncture from those taken through a venous catheter. When the former is negative, but the latter is positive, this may represent contamination. These factors are likely to diminish the quality of data and lead to an overestimate of CLABSI infections if surveillance of haematology patients is based upon the current NHSN definition. These limitations are acknowledged in Queensland surveillance guidelines, where bacteraemia associated with febrile neutropenia is excluded.5

Application of the NHSN CLABSI definition to ICU populations in Australia has shown poor inter-rater reliability and sensitivity,6 limiting the extent to which surveillance data can be used as a reliable quality indicator.7 These pitfalls are likely also to be present in non-ICU populations, including haematology patients.

Recent guidelines published by the Australian Commission on Safety and Quality in Health Care propose that bloodstream infections associated with mucositis be excluded from CLABSI surveillance strategies.4 This is one step forward. However, further developments to address the other issues identified earlier are needed for a valid CLABSI case definition in this population. These refinements are necessary for data concerning haematology patients to be compared consistently over time within individual healthcare facilities, and for comparison of infection rates across centres. Only then will the true impact of preventive strategies be adequately assessed.

Addendum: Since the letter was written, the NHSN have published new guidelines that recognise a separate category of CLABSI associated with mucosal barrier injury to particularly address the issue of mucositis in haematology patients.

Received 24 September 2012; accepted 23 October 2012.

doi:10.1111/imj.12027

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References

Letters to the Editor

Author reply

We thank Worth and colleagues'1 interest and comments on our publication.2 We agree that the existing definitions of central venous catheter-associated blood stream infection (CLABSI) including those of the Australian Commission on Safety and Quality on Health Care are inadequate for describing CLABSI in haematomatological patients. We support their suggestions to instigate further refinements to the definitions of CLABSI as it will improve uniformity in reporting of this type of infection. This will assist in delineating those infections that are healthcare acquired in this patient population, and foster the implementation and evaluation of infection control efforts.

Received 31 January 2013; accepted 4 February 2013.

doi:10.1111/imj.12091

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Telerheumatology: not ready for prime time

Roberts et al. suggest telerheumatology as a solution to the national shortage of rheumatologists in Australia.1 Gray et al. extolled a similar approach to extending access to expertise in geriatric medicine.3 Indeed, chart review by geriatricians has contributed greatly to the quality of geriatric care. Interactive interview and discussion of diagnosis and treatment of individual patients allow significant contribution to standard of care, as participants have the necessary history taking and physical diagnosis skills. That assumption of participant skills is reasonable for the required general medicine aspects of geriatric consultations,4 not so much for the required rheumatologic skills.

I cannot speak on the extent of musculoskeletal and rheumatologic training of medical students and primary care physicians in Australia.5,6 However, such training in the United States is quite limited and seems inadequate to the process.1,6 Absenting substantial revision of medical school and postgraduate education and training, telerheumatology does not seem feasible. The scope of medicine as well as the necessary database has greatly expanded over the past several decades, while time allotted has not. Actually, in US training programmes, it has decreased, with restriction of trainee hours.

Recognising the substantial difference between hospital and outpatient medicine, training related in the former setting provides only limited preparation for the latter. Given the heavy hospital-based bias of training programmes and limited economic support and opportunity for specialist mentoring in the outpatient/office/clinical practice setting, one might question the preparedness for clinical practice, even in the more insightful family medicine programmes. The latter have early on recognised the issue, but time and specialist mentoring limitations are still problematic. Perhaps, expanding training programmes from 3 to 5 years would solve most of the challenges, but little interest has been expressed in doing so. Such an approach might provide capable participants for telerheumatology, but at this time, I must respectfully disagree with the suggestion by Roberts et al.,1 and suggest that telerheumatology is an idea whose time has not yet come.

Roberts et al. appropriately note the logistic and economic challenge related to current rheumatologic care access.1 The expense of travel (both time and cost) is substantial, when indeed it is even feasible. Hopefully, treatment should interfere less than the patient’s disease with activities of daily living. One aspect is the process involved for access to care, such as having the rheumatologist travel to remote sites. An alternative would be time-effective for the rheumatologist, but telerheumatology does not yet have the necessary ‘support base’ (participants adequately trained/educated in the rheumatologic approach). I would suggest rather that the time has come for amending training programmes and other postgraduate education to correct the lapses in rheumatologic education of the primary physician.

Received 25 October 2012; accepted 12 November 2012.

doi:10.1111/imj.12052

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References


Author reply

Rothschild rightly laments the insufficient undergraduate and primary care musculoskeletal training in the USA, a situation replicated in Australia. This means that an adept musculoskeletal examination will generally be unavailable at the patient end in telerheumatology consultations. To address this by attempting to train and upskill a community-based workforce would take many years, high levels of sustained commitment, and substantial resources.

While acknowledging this skill shortage, we feel that telerheumatology is already a useful model as a complement to face-to-face consultations. That is, for the many patients where travel time is considerable, some, but not all, of the consultations are better done using telerheumatology. A list of clinical situations that might be suitable for telerheumatology consultation is provided in our original article. The potential scope of telerheumatology has also been expanded by advances in patient-reported outcome measures in rheumatoid arthritis, such as the validated Routine Assessment of Patient Index Data 3 which removes the need for expert examination in a percentage of consultations.

Even though there are cost savings and convenience benefits, the primary aim of telerheumatology is to provide at least equivalent or improved quality of patient care by reducing the burden of access. As a more extreme example, one author (LJR) has a patient with rheumatoid arthritis who, prior to telerheumatology, drove 16 h each way for a 15-min review appointment every few months; the patient now does this every 1–2 years. So the question is no longer whether telerheumatology is valuable but rather in which patients.

Received 28 January 2013; accepted 5 February 2013.

doi:10.1111/imj.12099

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Mesiotemporal neuroimaging abnormalities in neurosyphilis and other causes of limbic encephalitis

It is to Saunderson and Chan’s credit that they raise awareness of the potential for syphilis (‘the great imitator’) to imitate herpes simplex encephalitis (HSE) radiologically.1

However, it is incorrect to assert, as they do, that the mesial temporal abnormalities their patient demonstrates are otherwise ‘pathognomonic’ for HSE. Apart from HSE and neurosyphilis, identical changes can be seen in ‘limbic encephalitis’ caused by several infective and (especially) autoimmune processes.2 Of particular pertinence is the growing number of antibody-mediated limbic encephalitis, such as the anti-N-methyl-D-aspartate receptor3 and the anti-leucine-rich glioma-inactivated-1 encephalitis.4 As immunosuppressives are usually used to treat these conditions, Saunderson and Chan’s report1 is a timely reminder that not all herpes simplex virus-negative limbic encephalitis is of autoimmune aetiology.

They also state that the magnetic resonance imaging (MRI) changes seen in neurosyphilis may be ‘indistinguishable’ from HSE. However, they do not mention whether or not their case (or others reviewed) demonstrated restricted diffusion on MRI, which is usually evident in cases of HSE5 and helps distinguish HSE from the autoimmune limbic encephalitides.

Received 10 October 2012; accepted 6 November 2012.

doi:10.1111/imj.12053

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4 Lai M, Huijbers MG, Lancaster E, Graus F, Bataller L, Balice-Gordon R et al.

Author reply

Kleinig1 raised an important point concerning our recent publication describing mesiotemporal changes on magnetic resonance imaging (MRI) in neurosyphilis.2

Kleinig1 has correctly asserted that the radiological changes seen in herpes simplex encephalitis can also be seen in ‘limbic encephalitis’ caused by several infective and autoimmune processes.

We certainly agree that mesiotemporal changes on MRI can indeed be seen in other conditions, including those mentioned by Kleinig, and in addition can also be seen in systemic lupus erythematosus, epileptic disorders, neurodegenerative disorders, neoplastic conditions (gliomatosis cerebri), metabolic disorders, vascular disorders and other disorders covered in Dalmau and Bataller, Sureka et al., Yokozeki et al. and Rubio-Agusti et al.3–6 Therefore, by strict definition, mesiotemporal changes are not ‘pathognomonic’ for herpes simplex encephalitis, but certainly traditionally the classic finding of mesiotemporal changes on MRI has been considered ‘virtually pathognomonic’ for herpes simplex encephalitis. However, increasingly the differential diagnosis is expanding to include the other entities outlined earlier. Certainly it seems that herpes simplex encephalitis remains the most common cause of these image changes.4

Unfortunately, the information regarding restricted diffusion was not available for all cases reviewed; however, our case, and many of the cases reviewed, did demonstrate restricted diffusion on MRI, making differentiation from herpes simplex encephalitis difficult on image findings alone. This highlights the importance of including neurosyphilis in the differential diagnosis when changes usually seen in herpes simplex encephalitis are detected on MRI, and where clinically indicated, excluding other relevant differential diagnosis.

Received 29 January 2013; accepted 30 January 2013.

doi:10.1111/imj.12092

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Letters to the Editor

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Rapid death after hospitalisation

In their audit of deaths within 24 h after admission to an inpatient palliative care unit, Paratz and Flynn highlight an important sub-population in the hospital system. However, their work only examines deaths in those admitted to a palliative care unit, and it is important to read this work in the broader context of death in the whole hospital system. An audit of three large South Australian hospitals demonstrated that 35% of all inpatients required a ‘palliative approach’ to their care, of whom only 22% were known to specialist palliative care services (SPCS).

Australian data suggest that 52% of all deaths occur in hospital. A Melbourne study found that 75% inpatient deaths were ‘expected’, and in this setting 38% had involvement of SPCS.

A palliative care approach aims to improve the quality of life of individuals facing life-threatening illness and of their families, by preventing and relieving suffering through early identification, assessment and treatment of pain and other problems – physical, psychosocial, and spiritual.

Rapid death after admission to hospital is not necessarily a poor outcome for patients, carers or families. There is a proportion of patients who desire their site of care to be home for as long as possible, but their site of death to be in a hospital or hospice setting. Therefore, timely transfer of these patients into inpatient care, even when close to death, may be a desired outcome.

Therefore, it is crucial to address end-of-life care issues in the context of all people dying an expected death to ensure quality care. Not all dying patients need SPCS; however, we should strive for a good quality of death for all. Further work is required to look at the care of those dying within 24 h of admission to hospital, not just palliative care units, in order to understand the impact of this on patients, carers and families.

Received 31 October 2012; accepted 21 November 2012.
doi:10.1111/imj.12051

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We wish to point out to readers that the letter that was published in the November 2012 issue of the Journal by Paix entitled: ‘Correcting Morris et al. with respect to anaesthesia for neonatal circumcision’ (Intern Med J 2012; 42: 1276–77) appeared as submitted by the author. Any implications about the original work or the reply by Morris by this wording were unintentional.

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