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And so, dear readers, another year has begun, and it is time for me to reflect personally on the one just gone. For the *Internal Medicine Journal* (IMJ), 2013 was a fabulous year: another near-record number of published pages, almost complete catch-up for manuscripts that had had delayed publication because of lack of space and a positive bump of the Citation Index (more of which below). The increased pages that were graciously provided by Wiley-Blackwell, our publisher, to start the process in 2012 continued in the year just passed, and I personally thank them for enabling us to start 2014 on a promising footing for timely publication of increasingly good material. At 140 pages, the May 2013 issue was the largest we have ever published for a standard print issue.

Authors are particularly interested in the time to publication along with the impact factor of the journal to which they submit their work. For the last issue for which I have data at the time of writing, our October issue had a median time to publication from acceptance of 110 days for the eight Original Articles and 149 days for the five Brief Communications. The upper ranges of these times (137 days and 258 days respectively) represent the final part of catching up on previously accepted manuscripts. By way of comparison, the equivalent delay for the October 2010 issue Original Articles was 439 days with a maximum of 537! I think this is clear evidence of improvement and we will get even better.

The impact factor improved as did our rating in the ‘league table’ of journals in the category of Medicine, General and Internal. As I have previously described, the impact factor is calculated based on citations in the previous 2 years (in this case, 2011 and 2012) during which time our denominator (number of citable articles) was significantly increased by the increased page count. Despite this, our impact factor improved from 1.541 in 2011 to 1.823 (and our ranking improved 10 places to 45/151) based on 253 citable papers published in 2010–2011.

The full-text download rate for IMJ papers continues to increase exponentially. In 2012, there were over 200 000 such downloads with broad international origins of the requests. The most downloaded paper published in 2012 was by Wright *et al.* on stroke management while the top-cited paper in the Journal during this period was the review by Scott and Jayathissa on quality drug prescribing.

We had a very stable Editorial Board in 2012 as we did for most of 2013: however, two of our long-serving and very productive editors left us in the last quarter of the year gone by. I wish Associate Professor Peter Gates (Neurology Editor since 2004) and Dr John Vinen (Emergency Medicine Editor since 1998) the very best for their personal and professional futures and you can watch the front pages for their replacements this year. Peter’s proactive commissioning of reviews and editorials leaves an exemplary model for his successor, and it is noteworthy that his paper describing brain-stem anatomy and vascular syndromes for the non-neurologist was one of the most accessed articles in 2013 and has been so since its publication in 2005. I cannot emphasise strongly enough how important is the dedication and selfless work for the Journal performed by each member of the Editorial Board.

Virginia Savickis, Editorial Manager, and Lorelie Willoughby, Editorial Office Administrator, have worked at double intensity over the past 2 years to get all of those extra pages filled accurately and with the right mix of content. My thanks to them continue to multiply year after year.

2013 saw the start of a specially commissioned collaborative series of seven proposed papers on telehealth commencing in the May issue with the publication of a paper by Sabesan *et al.* discussing which patients may be suitable for telehealth. The series, developed by the RACP Telehealth Working Group, is chaired by our Ethics editor, Professor Paul Komesaroff, and explores ways of delivering clinical care by physicians.

I might also mention that with the clearance of the publication backlog, it is anticipated to reactivate the Ethics series in the Journal with preliminary discussions in the last months of 2013 initiating contemporary pertinent topics for later publication.

If you have not done so already, please subscribe to receive the table of contents to be provided to you automatically to be alerted to newly published papers in the timeliest way. You can sign up at Wiley Online Library at http://onlinelibrary.wiley.com/journal/10.1111/(ISSN) 1445-5994, or for Fellows of the College via the publications link at http://www.racp.edu.au.

The Royal Australasian College of Physicians began a process of reorganisation and modernisation in 2013 and much will be achieved during 2014. The Adult Medicine Division has invited me to participate in its Council meetings over the year, and I have had the opportunity to...
present progress reports at each of these meetings. I think it is clear that the College is intensely interested in the future of the Journal and a publications working party of the Division is considering ways to improve it (and other College publications) in the future. I am delighted that we are part of the dialogue and would encourage any interested Fellows to tell the College if they have an opinion on the future direction of the Journal – or you can tell me!

Also of note, I would like to point out the special logo on the Journal’s cover and preliminary pages in recognition of the College’s 75th anniversary in 2013. One or two papers by editors are planned to commemorate some retrospective glimpses of the Journal before the May 2014 issue is published.

As always, I wish to thank in no meagre terms our manuscript reviewers. Like most of us, these are busy people (who else do you ask to do important and difficult work but those who do not have the time to do it). True to past performance, they have continued to produce a very high standard of review that has improved papers we have published or assisted unsuccessful authors in getting their work published elsewhere. Please read their names listed after this piece and find some way to thank them for their highly valued efforts especially if you have been or anticipate being an author.

I have no doubt that this year will once again produce challenges for us who produce this publication. With your help as authors and readers, we can continue the steady march to ongoing improvement and continued contribution to the education of the medical community.

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J. Szer
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New imaging techniques for more effective treatment in glioblastoma

High-grade brain tumours have a poor prognosis, indeed as few as 16% of patients with glioblastoma survive 2 years post diagnosis.\(^1\) Over half of glioblastoma incidence is in the productive years of life,\(^2\) when in employment and often with young children. Thus, even a small improvement in the outcome of treatment can result in significant benefit not just to patients, but also to the community and to the economy.

Unlike other cancer sites (such as breast and prostate) treatments in this area have been slow to evolve. The use of temozolomide and more conformal radiotherapy techniques has certainly improved survival.\(^3\) There are several new potential treatments but due to the heterogeneous and phenotypically variable nature of glioblastoma, these are unlikely to provide a significant benefit for many of the patients diagnosed. New treatments are expensive for pharmaceutical companies to develop and for governments to fund. Many novel agents do not even make it to phase III studies, and new methods of rapidly screening potential agents are urgently needed. We believe new methods of brain imaging constitute a rapid and clinically valid method both to assess treatment and to provide information on which patients are most likely to benefit.

The hypothesis of one mutation being useful in treating a tumour has been revolutionary for some less complex tumours. However, it is unlikely to provide long-term gains with glioblastoma. This is partly because the stromal environment and the random de-differentiation of stem cells and their biology are complex. But clustering analysis now suggests that the clinical entity of glioblastoma can be molecularly divided into at least six main groups.\(^4\) This presents difficulties for performing clinical trials.

A further issue that hinders development in glioblastoma is that it constitutes only 1% of the total tumour burden. Most cancer treatment centres in Australia and New Zealand are unlikely to treat more than 40 glioblastoma patients a year, presenting a problem for trials with very tight eligibility. This is especially so when the small number has to be analysed according to the groups of genetic characteristics associated with different survival. Similarly, ‘salvage’ therapy trials present problems as the clinical state of patients decline rapidly.

In addition, in all new cancer therapy development the drug discovery process is expensive and slow. Specifically with glioblastoma, there have been no new systemic agents for a large period of time apart from temozolomide. With the survival at 2 years of 16% the 10 years plus of potential drug development is too long. Patients rarely survive long enough to have a second attempt at radical treatment.

As existing radiological response criteria using computed tomography and magnetic resonance imaging (MRI) (e.g. McDonald criteria) are difficult to interpret for a prolonged period after glioblastoma treatment (reducing the ability to assess responses to treatment), rapid and accurate surrogate markers that correlate with survival are needed here. Functional (metabolic) imaging with positron emission tomography (PET) is one such potential methodology. PET can look at multiple facets of tumour biology with exquisite resolution and with tracers present in picomolar concentrations.\(^5\) Concurrent MRI may provide even more useful information as we learn more about how to interpret the images.\(^6\)

This metabolic imaging is helpful in a number of ways. First, it informs us when a tumour is undergoing genetic changes, enabling treatment to be changed early. It also enables mechanisms of tumour resistance to be investigated, such as tumour hypoxia using \(^{18}\)F-misonidazole. It can help in identifying reducing treatment resistance, therefore enabling a change in therapy. This is important as it is known from other tumour sites (such as non-small cell lung cancer) that resistance to single-agent targeted therapy develops increasingly quickly as patients move from first- to second-line therapy. Metabolic imaging could enable us to study the effects of novel treatment regimens such as the use of multiple agents earlier in treatment or in combination, or at different times during the treatment cycle, enabling an expedited drug discovery, phase I and phase II trial stages. If this surrogate outcome is directly correlated with clinical outcomes, imaging could also reduce the need for expensive and hard to recruit phase III clinical trials.\(^7\) However the acceptance of a surrogate outcome for a novel agent would have to meet the rigorous requirements of regulatory authorities to enable registration, although this may be different for repurposing of older agents. It is thus still likely that although the imaging correlates with survival, the measure of success required to enable registration would remain patient outcomes.
Also, the measurement of success in treatment is all performed non-invasively. It is likely that more reliable PET imaging may decrease the need for routine surveillance imaging such as MRI. PET could guide emerging radiation techniques such as ‘dose painting’, which may help in locally intensifying treatment, reducing toxicity to surrounding normal tissue.

Last, multiple attempts over many years and many different tumour types have been made to predict tumour response in vitro, with little correlation to clinical response. New hybrid clinical imaging technology, such as PET-MR, has the advantage that it is in vivo and avoids the problems of an experimental tumour model. Investigation with PET end-points could open new therapeutic options, much more cost-effective than developing a drug to phase II trial stage that may have no clinically relevant effect despite blocking the putative receptor. An unexplored but potentially useful aspect of this platform is thus to enable re-examination of old drugs with recently found effects on cancer pathways. However, this research is not ‘novel’ or scientifically exciting, and therefore philanthropic donors and governments must take the leadership in funding here.

Australia will install its first combined PET-MR scanners early in 2014. The concept of multidisciplinary groups spanning the disciplines of chemistry, physics, image analysis, nuclear medicine, radiology, oncology and pharmacology to identify rapidly agents that affect a known surrogate outcome in glioblastoma has arrived. We need to take advantage of this window in research internationally to change the paradigm of brain tumour treatment.

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References

REVIEW

How to diagnose amyloidosis

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Key words
amyloidosis, diagnosis, immunohistochemistry, genetic testing, proteomics.

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Abstract
Amyloidosis is a rare but devastating condition caused by deposition of misfolded proteins as aggregates in the extracellular tissues of the body, leading to impairment of organ function. High clinical suspicion is required to facilitate early diagnosis. Correct identification of the causal amyloid protein is absolutely crucial for clinical management in order to avoid misdiagnosis and inappropriate, potentially harmful treatment, to assess prognosis, and to offer genetic counselling if relevant. This review summarises the current evidence on which the diagnosis and subtyping of amyloidosis is based, outlines the limitations of various diagnostic techniques, particularly in an Australian and New Zealand context, and discusses optimal strategies for the diagnostic approach to these patients. Recommendations are provided for when particularly to suspect amyloidosis, what investigations are required, as well as an approach to accurate subtyping of amyloidosis.

Introduction
For the majority of physicians, amyloidosis is a mysterious disease, often only considered following an unexpected pathology report. Over the years, variations in classification systems have not helped the understanding of the disease. This is a pity because fundamentally amyloidosis is a simple disease characterised by tissue deposition of a protein able to assume an insoluble beta-pleated sheet structure. This tissue deposition ultimately interferes with normal organ function. The physician faced with a patient with a new diagnosis of amyloidosis initially must ask himself or herself only three important questions: what is the protein that is causing the amyloidosis, where is it being produced, and finally, in what tissues of the body is it being deposited? All therapeutic decisions will logically follow.

Approximately 25 proteins currently are recognised to cause amyloidosis and the amyloidogenic protein is the basis for the current classification (Table 1). Each type of amyloid has the prefix ‘A’, for amyloid, followed by an abbreviation derived from the name of the protein; thus, AL designates amyloid derived from immunoglobulin light chain, ATTR is amyloid derived from transthyretin (TTR), AFib indicates amyloid derived from fibrinogen,

etc. In amyloidosis, these normally soluble proteins misfold and aggregate to form protofilaments and fibrils by virtue of a common cross beta-pleated sheet structure. The fibrils then co-deposit in the extracellular space with serum amyloid P protein (SAP) and other components, such as glycosaminoglycans, to form the insoluble amyloid deposits.

Like a group of naughty children, each amyloid-producing protein produces its own form of mischief. Some cause chaos rapidly, others in a slower but nevertheless relentless fashion. Some have predilections for particular organs such as the myocardium, the kidneys or the nerves. It can be difficult to recognise these patterns outside the few centres reviewing large numbers of patients with this rare disease and therefore centralised review if not management of all such patients should be considered. In the meantime, amyloid can be demystified. The aim of this paper is to provide physicians with a framework for the assessment and diagnosis of suspected and proven amyloidosis. Management of amyloidosis is beyond the scope of this article, and readers are referred to recent reviews on this topic.11,12

When to suspect amyloidosis
Amyloidosis can present with a bewildering array of symptoms depending on the organs involved (Fig. 1). Initial symptoms are often non-specific, such as fatigue
<table>
<thead>
<tr>
<th>Amyloid type</th>
<th>Other names</th>
<th>Protein</th>
<th>Mechanism</th>
<th>Organs involved</th>
<th>Associated disease/population</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Primary (no longer favoured terminology)</td>
<td>Monoclonal Ig light chains</td>
<td>Acquired, abnormal, amyloid-forming protein</td>
<td>++++</td>
<td>Acquired factor X deficiency ++†</td>
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<td>++</td>
<td>Plasma cell dyscrasias/older people</td>
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<td></td>
<td></td>
<td>++‡</td>
<td>Any cause of systemic inflammation</td>
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<td></td>
<td></td>
<td>++§</td>
<td>Dialysis</td>
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<td>AA&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Secondary/reactive (no longer favoured terminology)</td>
<td>Serum amyloid A</td>
<td>Normal protein at supra-normal concentration</td>
<td>++++</td>
<td>NA</td>
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<td></td>
<td>++</td>
<td>Any cause of systemic inflammation</td>
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<td></td>
<td>—</td>
<td>Carpal tunnel syndrome +++</td>
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<td>—</td>
<td>Different population groups depending on mutation</td>
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<tr>
<td>AB&lt;sub&gt;2&lt;/sub&gt;M&lt;sup&gt;3&lt;/sup&gt;</td>
<td>DRA (dialysis related amyloidosis)</td>
<td>Beta-2 microglobulin</td>
<td>Normal protein at supra-normal concentration</td>
<td>— — — — — ++++§</td>
<td>NA</td>
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<td>ATTRwt&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Senile systemic (cardiac) amyloidosis</td>
<td>Transthyretin (wild type)</td>
<td>Normal protein, normal concentration, prolonged exposure</td>
<td>— ++++</td>
<td>Carpal tunnel syndrome +++</td>
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<td>Carpal tunnel syndrome +++</td>
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<td>Different population groups depending on mutation</td>
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<tr>
<td>ATTRm&lt;sup&gt;5&lt;/sup&gt;</td>
<td>FAP or FAC (familial amyloid polyneuropathy/ cardiomyopathy)</td>
<td>Transthyretin (mutated)</td>
<td>Hereditary, mutant protein</td>
<td>+ +++</td>
<td>Leptomeningeal + Vitreous opacities +</td>
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<td>Different population groups depending on mutation</td>
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<td>AFib&lt;sup&gt;6&lt;/sup&gt;</td>
<td>NA</td>
<td>Fibrinogen A-alpha chain</td>
<td>Hereditary, mutant protein</td>
<td>++++</td>
<td>NA</td>
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<td>NA</td>
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<td>ALys&lt;sup&gt;7&lt;/sup&gt;</td>
<td>NA</td>
<td>Lysozyme</td>
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<td>Splenic rupture</td>
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<td>AAPoA1&lt;sup&gt;8&lt;/sup&gt; and 2&lt;sup&gt;9&lt;/sup&gt;</td>
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<td>Apolipoproteins 1 and 2</td>
<td>Hereditary, mutant protein</td>
<td>++++</td>
<td>NA</td>
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<tr>
<td>ALect2&lt;sup&gt;9&lt;/sup&gt;</td>
<td>NA</td>
<td>Leukocyte chemotactic factor 2</td>
<td>Hereditary, mutant protein</td>
<td>++++</td>
<td>Hispanic Americans</td>
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<td>AGel&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Finnish; Meretoja syndrome</td>
<td>Gelsolin</td>
<td>Hereditary, mutant protein</td>
<td>— — — — Cranial neuropathy +++†</td>
<td>Corneal lattice dystrophy +++</td>
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+++ 50–100%; ++, 25–50%; +, 10–25%; +, <10%; -, organ involvement not reported or uncommon. †Symptomatic macroglossia and skeletal muscle involvement are highly suggestive of the AL subtype. ‡Factor X deficiency (or, rarely, other factors) has only been reported in AL subtype. §Amyloid deposits in bone cysts and joint synovium. ¶Facial paresis, also often associated with a sensory peripheral neuropathy. GIT, gastrointestinal tract; NA, not applicable.
and weight loss, but as the disease progresses, symptomatology reflects the impairment of the organs involved by the amyloidosis. Certain clinical presentations require a diagnosis of amyloidosis to be considered (Table 2). These include nephrotic range proteinuria, cardiac failure with left ventricular hypertrophy in the absence of hypertension or aortic valve disease, sensorimotor peripheral neuropathy without obvious cause, and hepatomegaly with a normal appearance on ultrasound or computed tomography (CT) imaging. As the most common type of amyloidosis is AL, the combination of an appropriate clinical scenario and an immunoglobulin free light chain (FLC) abnormality (see later discussion) provides a high suspicion of AL amyloidosis necessitating further histological investigation.

The amyloidoses are most often systemic that is where the production of the amyloid-forming protein is distant to the amyloid deposits (e.g., monoclonal immunoglobulin production in the bone marrow depositing as amyloid in the heart, or variant fibrinogen produced in the liver depositing as amyloid in the kidney). Localised amyloidosis, amyloid deposits occurring only at the site of amyloid-forming protein production, is another well-recognised entity. Localised amyloidosis has a range of well-recognised presentations, particularly those because of localised AL amyloid that is a non-life-threatening disease with rare progression to systemic AL amyloidosis.

Table 2 More common clinical scenarios where amyloidosis should be suspected

<table>
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<td>Nephrotic range proteinuria</td>
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<td>Cardiac failure with left ventricular hypertrophy in the absence of hypertension or aortic valve disease</td>
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<td>Sensorimotor peripheral neuropathy without obvious cause</td>
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<td>Hepatomegaly with a normal appearance on ultrasound or computed tomography imaging</td>
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<td>Autonomic neuropathy</td>
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Figure 1 Organ involvement in common subtypes of amyloidosis (+++, 50–100%; ++, 25–50%; +, 10–25%; +, <10%). Illustration modified from Anatomica, the complete home medical reference and used with permission from Global Book Publishing. AFib, amyloid derived from fibrinogen; AL, amyloid derived from immunoglobulin light chain; ATTR, amyloid derived from transthyretin.
but frequent local recurrences. Localised amyloidosis results from the local production and deposition of amyloidogeneic proteins, with AL type deposits thought to be produced by foci of low-grade monoclonal B-cells or plasma cells that secrete monoclonal immunoglobulin light chains in the immediate vicinity. These amyloid deposits are commonly located in the airways (including nasopharynx, larynx and bronchi) and lungs, orbit and adnexae, bladder, gastrointestinal tract, lymph nodes, and skin. Localised amyloidosis can and has been reported to occur in almost any organ of the body. It is also seen infiltrating plasmacytomas and, in this situation, is not necessarily indicative of systemic disease. Occasionally localised amyloid can be seen in the skin comprised of insulin around injection sites of insulin-dependent diabetics or of keratin in areas of excoriation or trauma.

**Making the diagnosis of amyloidosis**

The diagnosis of amyloidosis requires a tissue biopsy. To date, the gold standard test for histological confirmation of amyloid deposits is the Congo red stain used in conjunction with polarised light microscopy. Congo red results in a pale ‘salmon-pink’ staining that shows typical birefringence and dichroism effects when examined under polarised light microscopy (Fig. 2). It is essential that a reliable staining protocol is used to avoid non-specific staining. In some cases, multiple sections may need to be examined as amyloid deposits can be focal and irregularly distributed. In circumstances where there is a high index of suspicion for amyloidosis and Congo red appears to be negative, an alternative dye such as crystal violet may be used but can be non-specific. The fact that SAP, which is a normal plasma glycoprotein, is present in all types of amyloid, has been exploited to aid in the diagnosis of amyloid by immunohistochemistry, but the staining pattern that is obtained with antibodies to SAP can be difficult to interpret. Hence, this test should not be used in isolation for the diagnosis of amyloidosis. Electron microscopy (EM) is often used in conjunction with histology for the diagnosis of amyloidosis, although this is not always necessary. Ultrastructurally, amyloid deposits are composed of haphazardly distributed, non-branching fibrils with a mean diameter of 10 nm (range 8–12 nm) and an electron-lucent core. This feature is characteristic, but not specific, as fibril deposition may be seen as other conditions, such as fibrillary glomerulonephritis, immunotactoid glomerulonephritis, glomerular sclerosis, diabetic fibrillosis, fibronectin glomerulopathy and collagenofibrotic glomerulopathy. These are differentiated according to fibril appearance and diameter, and the findings should be interpreted in conjunction with those of light microscopy, Congo red staining and immunofluorescence or immunohistochemistry.

Not all monoclonal immunoglobulin deposition in the tissues is due to amyloidosis. In rare cases, monoclonal immunoglobulin can be deposited particularly in the kidneys in a non-amyloid form. These diseases (e.g. light and heavy chain deposition disease) do not have the typical Congo red staining under polarised light, have a tendency towards kappa rather than lambda light chain deposition and in general have more restricted organ involvement than AL amyloid with which they are often confused. Like AL amyloid, however, they are frequently associated with myeloma or other lymphoproliferative diseases.

**What to biopsy**

For the diagnosis of amyloidosis, biopsy of the clinically involved organ is the most sensitive method and has the advantages of providing larger amounts of tissue for subsequent subtyping and detecting concomitant pathologies. However, such biopsies can be associated with discomfort and the morbidity of bleeding and rarely organ perforation. Thus, if amyloidosis is suspected, a less invasive biopsy may be preferred and can be taken from...
a distant site such as the abdominal fat, bone marrow, rectum, gingiva or minor salivary glands. Reports from reference centres suggest high sensitivity – for example, amyloid deposits can be detected in the bone marrow trephine in 70% of cases\textsuperscript{23} and in fat pad (aspirate or biopsy) and rectal biopsies in over 80%\textsuperscript{23,24} – but in our experience, this is difficult to replicate in more general settings.\textsuperscript{25} Amyloid deposits on such screening biopsies are often very small, and there is the disadvantage of limited material for subsequent subtyping that may necessitate the need for further biopsy. Nevertheless, abdominal fat pad aspiration has been used increasingly in recent years, and a description and instructional video of the procedure can be found online.\textsuperscript{26} Careful collaboration with the pathology service is required when setting up this procedure. If initial screening biopsies are negative and the clinical suspicion of amyloidosis is high, then screening biopsies may need to be repeated or the clinically affected organ should be biopsied.

**Key points related to diagnosis of amyloidosis**

- Early diagnosis is the key to effective management
- The diagnosis of amyloidosis requires a high index of clinical suspicion, particularly in certain clinical presentations (Table 2)
- Amyloidosis cannot be diagnosed without biopsy of either an affected organ or an amyloid-containing but clinically silent site
- Screening biopsy of abdominal fat may be useful to confirm the diagnosis and avoid biopsy of major organs, but sensitivity is only moderate
- Congo red staining of a biopsy sample remains the gold standard diagnostic test.

**Subtyping of amyloidosis: getting the diagnosis right**

Once amyloidosis is confirmed, it is of critical importance to identify the subtype accurately, as management differs substantially depending on the nature and source of the amyloid-forming protein ranging from supportive care through to aggressive chemotherapy or organ transplantation. The approach to subtyping has evolved dramatically over the last 30 years, moving from limited, uninformative histology stains through more specific immunohistochemistry supplemented by genetic analyses and, latterly, including direct identification of the amyloid-forming protein in biopsy specimens using tandem mass spectrometry. Every amyloid patient now can – and should – have his/her amyloid protein identified to a high level of confidence. This requires careful consideration of the patient’s presentation and phenotype, the presence or absence of associated diseases, and findings of histopathology, genetic testing and direct analysis of fibril proteins.

**Importance of clinical phenotype**

Systemic amyloidoses may affect any major organ, with the notable exception of the brain parenchyma, and the clinical phenotypes are therefore protean. Patients must therefore be assessed for organ involvement as there are some broad subtype–phenotype associations that help inform diagnosis of amyloid subtype and subsequent treatment choices. The clinical and laboratory/imaging features of involvement in various organs are summarised in Table 3. Work-up must include clinical assessment considering all the features in Table 3, in particular investigations of renal function (serum creatinine, 24-h proteinuria), heart (brain natriuretic peptide (BNP), troponin, electrocardiogram (ECG) and echocardiography) and liver (liver function tests and ultrasound scan for span if clinically uncertain).

For assessment of heart involvement by amyloid, the cardiac biomarkers are important. Similar to its role in heart failure, a N-terminal prohormone of BNP <332 ng/L effectively excludes important cardiac amyloid.\textsuperscript{27} Echocardiography remains an important screening tool, but it should be noted that the classic ‘speckled appearance’ in the myocardium is a late feature and its absence by no means excludes significant cardiac involvement. Typical features are a thick-walled left ventricle because of amyloid infiltration, a preserved ejection fraction, bialtrial enlargement and restrictive filling patterns on Doppler studies; however, no echocardiographic appearance is specific for amyloid heart disease. Cardiac magnetic resonance imaging (MRI) is a useful investigation in select cases to confirm the presence and potential severity of cardiac involvement in AL and ATTR,\textsuperscript{28} although significant renal dysfunction is a relative contraindication because of the rare risk of nephrogenic systemic sclerosis. Late gadolinium enhancement is a characteristic and relatively specific finding.\textsuperscript{29}

The relationship between clinical phenotype – that is, the patient and their organ involvement – and amyloid subtype is summarised in Table 1 and discussed briefly as follows.

- AL amyloidosis is more common in older patients as the incidence of monoclonal gammopathies, from which the amyloid-forming monoclonal immunoglobulin light chains are derived, increases with age. It can affect one or many organ systems, the multitude or pattern of which often makes other amyloidoses unlikely. Periorbital and other bruising perhaps because of the fragility of...
Amyloid-affected vessels are more common in AL amyloidosis than other subtypes; symptomatic macroglossia, skeletal muscle involvement and coagulation factor X deficiency, and subtle thickening of the tissues of the lower face are highly suggestive of AL amyloidosis but are each seen in only a small minority.1

• AA amyloidosis primarily affects the kidney with later involvement of the liver and sometimes the gastrointestinal tract. Symptomatic cardiac and nerve involvement are rare.2

• ATTR amyloidosis primarily affects the heart and peripheral and/or autonomic nervous system. The unmutated TTR molecule causes senile systemic amyloidosis (also known as senile cardiac amyloidosis) that has a cardiac-dominant presentation in the very elderly.4 There are at least 100 recognised mutations of the TTR molecule that increase its amyloidogenicity, understandably producing some phenotypic heterogeneity.3 The commonest mutation worldwide is the Ile122 that is found in ∼4% of west Africans (including African Americans) and causes slow-onset cardiac amyloidosis in the 7th and 8th decades.30 Many mutations, including Met30 and Ala60, are seen at low frequency in the Australasian population.5

<p>| Table 3 Investigating organ involvement in amyloidosis |
|----------------|---------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Organ</th>
<th>Clinical finding</th>
<th>Useful investigations and findings that suggest involvement</th>
<th>ISA consensus definition for organ involvement in AL amyloidosis†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>Oedema</td>
<td>Proteinuria, Renal failure, No particular imaging features</td>
<td>24-h urine protein &gt;500 mg/day, predominantly albumin</td>
</tr>
<tr>
<td>Heart</td>
<td>Breathlessness on exertion, Heart failure, Arrhythmias less common</td>
<td>Raised NT-ProBNP and/or troponin ECG often characteristic in AL, (low-voltage, poor R-wave progression), Echocardiograph: ventricular and valve thickening, bialtrial enlargement, diastolic physiology, MRI (late gadolinium enhancement characteristic)</td>
<td>NT-proBNP ≥332 ng/L, in the absence of renal failure or atrial fibrillation, Mean left ventricular wall thickness &gt;12 mm, no other cardiac cause</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatomegaly</td>
<td>Abnormal liver function, usually ALP/GGT</td>
<td>Span &gt;15 cm in the absence of heart failure</td>
</tr>
<tr>
<td>GIT</td>
<td>Symptoms can be difficult to distinguish from autonomic neuropathy, Gastrointestinal bleeding</td>
<td>No particular imaging features</td>
<td>ALP &gt;1.5 × ULN, Direct biopsy verification with symptoms</td>
</tr>
<tr>
<td>Nerve</td>
<td>Peripheral neuropathy (distal, symmetrical, sensory neuropathy; motor neuropathy uncommon in AL), Autonomic neuropathy (early satiety, irregular bowel habit, erectile dysfunction, postural hypotension)</td>
<td>Formal nerve conduction studies not usually helpful, Nerve biopsy, but do only if clinically important to establish involvement</td>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Macroglossia, Arthropathy, Claudication (vascular amyloid), Myopathy (pseudohypertrophy), Breathlessness, cough</td>
<td>Nerve biopsy, but do only if clinically important to establish involvement</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>Breathlessness, cough</td>
<td>CT, interstitial pattern (in absence of pulmonary oedema), Biopsy, but do only if clinically important to establish involvement</td>
<td>Interstitial radiographic pattern in absence of pulmonary oedema, Direct biopsy verification with symptoms</td>
</tr>
</tbody>
</table>

† Organs are considered involved if amyloid present in a biopsy of that organ (excluding blood vessels as the sole site of amyloid deposition), or proven in another site and meeting the clinical criteria above. ALP, alkaline phosphatase, CT, computed tomography; GGT, gamma glutamyl transpeptidase; GIT, gastrointestinal; ISA, International Society of Amyloidosis; NT-ProBNP, N-terminal prohormone of brain natriuretic peptide; ULN, upper limit of normal; USS, ultrasound scan.
A small number of centres internationally, but not in Australia or New Zealand, has access to targeted scintigraphy of amyloid deposits using I-131-labelled SAP.32 This allows identification of amyloid in larger viscera such as the kidneys, liver and spleen, as well as bones. Resolution is generally low, but the distribution of amyloid may provide a clue to amyloid type. While SAP scintigraphy is a very useful ancillary technique, the majority of diagnostic and monitoring information required for patient management can be gained from other investigations. The heart is also not imaged by this technique, but reports over many years suggest that technetium scintigraphy (e.g. technetium(99mTc)3,3-diphosphono-1,2-propanedicarboxylic acid) may allow identification of cardiac involvement.33

**Searching for associated diseases**

As one considers the patient and their phenotype, so must a search begin for any potentially associated diseases such as a plasma cell dyscrasia or chronic inflammation. However, it must be appreciated that association is not evidence of causality. For example, a monoclonal gammopathy of uncertain significance (MGUS, or benign paraprotein) is found in ∼3% of Australian adults in their 50s, rising to 9% in their 80s,34 so some patients with systemic amyloidosis will by chance have an MGUS that is coincidental to their non-AL amyloidosis.35 Conversely, not all cases of true AL amyloidosis have a paraprotein detectable by conventional serum protein electrophoresis. Screening for the immunoglobulin light chain abnormality that accompanies AL amyloidosis requires a combination of serum protein immunofixation electrophoresis, urine protein immunofixation electrophoresis and the serum free light chain (FLC) assay. A clonal abnormality (serum paraprotein in ∼80%, urine Bence-Jones proteinuria in ∼70% or abnormal FLC ratio in ∼75%)36 will be apparent in 95–99% of cases, and omission of one of these testing modalities produces a significant reduction in sensitivity.27,36 Nevertheless, 2–5% of true AL cases have no detectable paraprotein or FLC abnormality because of inability of these assays to detect very low levels of monoclonal FLCs among the normal polyclonal background.

Bone marrow aspirate and biopsy for quantitation of plasma cell burden is recommended only for those with suspected AL amyloidosis; additionally, occasionally the trephine biopsy may be a useful site in which to search for vascular or interstitial amyloid if its presence has not yet been proven. Cytogenetics (metaphase and/or fluorescence in situ hybridisation) are recommended only if there is a significant plasma cell burden. Bone imaging (skeletal survey, MRI or positron emission tomography, as appropriate) is indicated only if a plasma cell dyscrasia is identified and, along with other markers of aggressive plasma cell behaviour like hypercalcaemia and the plasma cell burden, allows one to determine whether the AL amyloidosis is due to an MGUS or myeloma.

The inflammation underlying AA amyloidosis can have many causes (Table 4).3 A careful clinical enquiry for evidence of chronic inflammatory arthropathy or bowel disease, infection and hereditary fever syndromes should be made. Systemic inflammation is usually present for many years before the clinical onset of AA amyloidosis, and its likelihood is, in general, related to the severity and longevity of the inflammatory process. The normal inflammatory protein serum amyloid A (SAA) is the amyloid-forming protein, and ideally, serum levels should be measured. However, in practice, this assay is not routinely available and the C-reactive protein is an adequate substitute. Serial measurements may be required if AA is suspected. In a small but well-recognised group of patients with proven AA amyloidosis, there is no identifiable inflammatory disease clinically.

**Role of genetic screening**

Although uncommon, a genetic cause for amyloidosis should be considered in all patients, as many cases have no family history because of incomplete penetrance, unrecongnised onset or death from other causes in previous generations. The exclusion of hereditary amyloidoses is often very useful in helping solidify the diagnosis of AL amyloidosis. Testing for most hereditary forms of amyloidosis is available in Australia (ATTR, AFib, ApoA1, ALys).

<table>
<thead>
<tr>
<th>Underlying disorders associated with AA amyloidosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic inflammatory arthritis</td>
<td>60%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>33%</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>17%</td>
</tr>
<tr>
<td>Chronic sepsis</td>
<td>15%</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>5%</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>4%</td>
</tr>
<tr>
<td>Complications of paraplegia (infected pressure sores, urinary infection)</td>
<td>2%</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1%</td>
</tr>
<tr>
<td>Periodic fever syndromes</td>
<td>9%</td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>5%</td>
</tr>
<tr>
<td>Crohn disease</td>
<td>5%</td>
</tr>
<tr>
<td>Other chronic inflammation</td>
<td>6%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1%</td>
</tr>
<tr>
<td>Castleman disease</td>
<td>2%</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>1%</td>
</tr>
<tr>
<td>Unknown</td>
<td>6%</td>
</tr>
</tbody>
</table>

Contact: Associate Professor David Booth, Pathology...
Approach.

The combination of a monoclonal immunoglobulin abnormality on serum or urine testing, and amyloid on a biopsy is highly suspicious but not diagnostic of AL amyloidosis.

Potassium permanganate pretreatment followed by Congo red staining is unreliable for subtyping and should no longer be used.

### Immunohistochemistry and other histological techniques

In most centres, apart from renal biopsies where there is the added luxury of a fresh frozen sample for direct immunofluorescence, the subtyping of amyloid is usually performed by immunohistochemical staining (IHC) of formalin-fixed paraffin-embedded (FFPE) tissues. Many laboratories report stains using antibodies to SAA, TTR, and kappa and lambda FLC. Although IHC, when well performed on optimally fixed and processed tissue, can be reliable in a significant percentage of cases, problems are not infrequently encountered even in the hands of international centres performing the technique frequently. Common problems include weak staining for $\kappa$ and $\lambda$ light chains in AL amyloidosis, false-positive staining of light chains in non-AL amyloid, background staining of light chains because of ‘locking-in’ of serum proteins during fixation, and false-positive staining for TTR in AL amyloidosis. False-negative and -positive results are common, and positive results for several different stains on a single biopsy specimen may be observed. Although other more reliable histological techniques are available, such as direct immunofluorescence on fresh frozen tissue samples and immuno-EM (only available in Italy), recent developments in the use of mass spectrometry (see later discussion) and its availability in both Australia and New Zealand mean that it has become the investigation of choice to resolve difficult cases where IHC is inconclusive or atypical. Clinicians treating patients with amyloid should be aware of the limitations of IHC and discuss difficult cases with their nearest amyloid referral centre. Where appropriate, a joint decision to refer biopsies for mass spectroscopy is the best approach.

### Tandem mass spectrometry

In the past decade, new methods have been developed that have enabled the use of FFPE tissues to be used in the study of proteomics by mass spectrometry, the first report being in 2005. Laser capture microdissection has been used to procure the usually small amounts of amyloid deposits and to ensure that the sample is relatively pure, with minimal protein contaminants present from the normal surrounding tissues. Advances in high-performance liquid chromatography and mass spectrometry technologies have led to greater sensitivity for low-level samples. This is particularly salient to the subtyping of amyloid, as in some biopsy samples, the amyloid deposits may only be present in a few blood vessels. Early reports of the use of laser capture microdissection and tandem mass spectrometry in clinical biopsy specimens suggest that this method will soon become the gold standard for accurate subtyping of amyloidosis. The technique can be used to identify any of the amyloid subtypes whether they be acquired or hereditary variants. Currently, tandem mass spectrometry-based techniques are available in the research setting in Australia (contact: Dr Patricia Renaut, Department of Anatomical Pathology, Princess Alexandra Hospital, Brisbane; Patricia_Renaut@health.qld.gov.au) and New Zealand (contact: Dr Hugh Goodman, Haematology Department, Waikato Hospital, Hamilton; hugh.goodman@waikatodhb.health.nz).

### Key points related to subtyping of amyloid

- Correct subtyping of amyloidosis is critical in all cases.
- The combination of a monoclonal immunoglobulin abnormality on serum or urine testing, and amyloid on a biopsy is highly suspicious but not diagnostic of AL amyloidosis.
- Potassium permanganate pretreatment followed by Congo red staining is unreliable for subtyping and should no longer be used.
Subtyping of amyloid using immunohistochemistry of biopsies may give false-positive or discrepant results. Subtyping of amyloid using mass spectroscopy is becoming the new gold standard and is available in Brisbane and Auckland on request. Assessment of clinical phenotype, associated diseases, immunohistochemistry, genetic testing and tandem mass spectrometry will allow identification of the type of amyloid (Fig. 3).

Overall approach to amyloid subtyping

An approach to subtyping is summarised in Figure 3. As tandem mass spectrometry is not yet routinely available and immunohistochemistry has limitations, amyloid subtyping currently requires a multidisciplinary synthesis of information. Fortunately, however, the multitudinous amyloid subtypes present as a smaller number of common scenarios.

First, how much proof is needed to diagnose AL amyloidosis? This is the commonest conundrum encountered as the diagnosis must be sufficiently certain to justify proceeding with chemotherapy. Most patients with amyloidosis and a paraprotein do have AL, but unfortunately, the absence of a routinely available high-quality confirmatory test means that assumptions must be made. Cases with a phenotype that is highly likely to be AL (e.g. the combination of heart, kidney and nerves, or a feature such as macroglossia or factor X deficiency) when present with a paraprotein can be treated as AL without further testing as long as other clues (e.g. family history, concurrent inflammatory illness) are not present. Cases with an ambivalent phenotype, even when a plasma cell dyscrasia is present, must be further investigated.

Second, isolated renal amyloidosis is common. Most are AL and have a plasma cell dyscrasia, but there may be clues to other subtypes that should be pursued. Fibrinogen gene testing should be considered, and many patients will need tandem mass spectrometry for a firm diagnosis.

Third, isolated cardiac amyloidosis, with or without neuropathy (peripheral and/or autonomic), can be a difficult problem, particularly in the elderly. In younger...
patients, the differential diagnosis is between AL and hereditary mutations of TTR (ATTRm) that is readily solved by TTR gene testing. In those over 60 years, both senile systemic/cardiac amyloidosis (wild-type TTR: ATTRwt) and (potentially coincidental) MGUS become increasingly common, and therefore, in the elderly with a cardiac +/− neuropathic phenotype, AL and ATTRwt cannot be distinguished reliably without tandem mass spectrometry.

There are many other patterns of phenotype, histology, associated diseases and other data, some of which may allow amyloid subtyping with confidence. Tandem mass spectrometry is an invaluable tool for diagnosis in cases of uncertainty. In the event of difficult cases, the authors are always happy to be contacted for advice.

**Conclusion**

Amyloidosis is a rare but important disease that must be suspected, especially when typical clinical presentations are present. Early diagnosis allows access to all treatment options before advanced organ dysfunction develops. Accurate subtyping is central to the management of amyloidosis. In certain cases, the diagnosis may require a series of advanced diagnostic techniques and experience to identify correctly the causative protein. However, accurate subtyping of the amyloid is critical for correct management of the patient and should be sought in all cases so that all patients can have their amyloid protein identified to a high level of confidence.

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How to diagnose amyloidosis

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Erectile dysfunction
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Key words
erectile dysfunction, phosphodiesterase type 5 inhibitor, alprostadil, intracavernosal injection, vacuum constriction device.

Abstract
In the past 30 years, advances in basic science have been instrumental in the evolution of the male sexual health treatment paradigm from a psychosexual model to a new model, which includes oral and intracavernosal injection pharmacotherapy, vacuum constriction devices and penile prostheses for the treatment of erectile dysfunction. This progress has coincided with an increased understanding of the nature of male sexual health problems, and epidemiological data that confirm that these problems are widely prevalent and the source of considerable morbidity, both for individuals and within relationships.

Introduction
Community-based epidemiological studies suggest that erectile dysfunction (ED), the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance, is a common disorder in men, affecting up to 52% of men between the ages of 40 and 70 years and is associated with reduced quality of life. It is now recognised that vascular disease of the penile arteries is the most common cause of ED, accounting for up to 80% of cases. The nitric oxide–cyclic guanosine-3′,5′-monophosphate (NO-cGMP) system is important in producing the arterial dilation and venous occlusion necessary to attain and sustain an erection. Abnormalities of this vasodilator system due to endothelial dysfunction are present in atherosclerosis and play an important role in the pathophysiology of ED. Phosphodiesterase type 5 (PDE5) inhibitor drugs, which inhibit the breakdown of cGMP producing vasodilation and improve endothelial cell function, are very effective in treating ED.

Epidemiology
Data from Australian, US and UK studies are similar, estimating the prevalence of complete ED as approximately 5% among 40-year-olds, 10% among men in their 60s, 15% among men in their 70s and 30–40% among men in their 80s. It is projected that, by 2025, 322 million men worldwide will have ED. Prevalence studies show that, when controlling for other factors, increasing age obesity, diabetes, hypertension, hyperlipidaemia and vascular disease are causative factors. Although the incidence of ED rises significantly with increasing age, recent studies indicate that 55–70% of men aged 77–79 years are sexually active. However, only half of the men who self-report ED are concerned about it.

Pathophysiology
Penile erection is a neurovascular phenomenon that requires dilation of penile vasculature, relaxation of smooth muscle, increased intracavernosal blood flow and normal veno-occlusive function. Penile vascular disease is the most common cause of organic ED and may involve several pathophysiological mechanisms, including impaired arterial inflow, impaired smooth-muscle cavernosal relaxation, chronic ischaemia-induced increased cavernosal smooth-muscle contraction, cavernosal fibrosis, veno-occlusive dysfunction and chronic or episodic hypoxaemia. Endothelial dysfunction appears to be the final common pathway for many cases of ED. ED may be an early manifestation of generalised endothelial dysfunction, and a predictor and a precursor of other
forms of cardiovascular disease. More than half of men with ED who have no cardiac symptoms have an abnormal stress test, and 40% have been found to have significant coronary artery disease when studied.

Apart from age, the main risk factors are those for vascular disease (smoking, diabetes mellitus, hypertension, abnormal lipid profile, obesity and lack of exercise).

Essentially, any condition that damages endothelial function can result in ED. Other factors include depression and endocrine disorders (Table 1).

### Diabetes mellitus

ED occurs at an earlier age in men with diabetes mellitus (DM) compared with men without DM, and the age-adjusted probability of complete ED is nearly three times higher. More than 50% of men develop ED within 10 years of being diagnosed with DM. The prevalence of ED increases with duration, poor glycaemic control and complications of DM, such as vascular and microvascular disease and neuropathies. Studies have revealed ED prevalence rates of 49% in patients with type 1 diabetes, and 34% and 24% of severe and mild to moderate ED, respectively, in patients with type 2 diabetes.

### Neurological disease

Many neurological disorders including spinal cord injury, multiple sclerosis and cavernous nerve damage following major pelvic cancer surgery, such as radical prostatectomy or anterior resection, commonly lead to ED.

### Endocrine disorders

Endocrine disorders, such as hypogonadism, hyperprolactinaemia and thyroid disease play a significant role in ED physiology. Testosterone regulates cavernosal nerve structure and function, nitric oxide synthase expression and activity, PED5 and corporal smooth-muscle cell growth and differentiation.

### Benign prostatic hyperplasia (BPH)

Men with BPH have a high prevalence of ED. The explanation for this association remains unclear, and the quality of life of men with BPH is reduced by its effects on sexual function. Although most men with ED have an underlying vascular cause, usually related to endothelial dysfunction, there is always a contributing, sometimes substantial, psychogenic component related to performance anxiety. Treatment of this component alone may be sufficient to restore normal erections.

### Diagnosis

A full history and thorough clinical examination of the patient are needed to:

- Confirm that the patient is suffering from ED and/or another sexual dysfunction, such as hypoactive desire or premature ejaculation
- Assess the severity of the condition
- Determine whether ED is psychogenic or organic in origin
- Identify risk factors or comorbid disease.
- Assess the fitness of the patient for resuming sexual activity.

Several questionnaires have been developed to score the erectile problem objectively. The short five-question form of the International Index of Erectile Function
Table 2. Sexual Health Inventory for Men (SHIM)

- **How do you rate your confidence that you could get and keep an erection?**
  - 1 (very low) – 5 (very high)

- **When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?**
  - 0 (no sexual activity) – 5 (almost always or always)

- **During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?**
  - 0 (did not attempt intercourse) – 5 (not difficult)

- **During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?**
  - 0 (did not attempt intercourse) – 5 (almost always or always)

- **When you attempted sexual intercourse, how often was it satisfactory for you?**
  - 0 (did not attempt intercourse) – 5 (almost always or always)

The questionnaire is self-administered by the patient at the initial consultation. A total <21 indicates ED.

ED, erectile dysfunction.

(IIEF), the IIEF-5 or Sexual Health Inventory for Men is useful for both diagnosis and assessment of response to treatment (Table 2).11

ED can be an early symptom of a significant systemic condition, such as diabetes mellitus or cardiovascular disease. Findings from the history and examination of the patient can be supplemented by investigations to identify the cause of erectile failure. The association between anxiety and ED should be established. Psychogenic ED is likely in younger men with no vascular risk factors who report an abrupt onset of ED and persistent early morning or nocturnal erections. Psychogenic ED can be caused by several problems, principally performance anxiety, but also guilt, depression, relationship problems, or fear and personal anxiety. Careful enquiry should be made about current medications, such as beta-blockers and thiazide diuretics and antidepressants, as well as the use of recreational drugs.

**Physical examination**

The examination of a man with ED will be directed, to a certain extent, by his history and should include assessment of the external genitalia, the endocrine and vascular systems, and the prostate gland in most patients. The penis should be carefully palpated to exclude the presence of fibrous Peyronie plaques and to check for phimosis. Prostatic induration or a palpable nodule should raise the suspicion of prostate cancer.

**Clinical investigations**

The degree to which men should undergo clinical investigation depends on the patient’s history and examination findings. General investigations include serum concentrations of total testosterone (before 11am), fasting glucose, fasting lipids and, in men over 50 years of age, prostate-specific antigen. Further investigations may be required based on the results of these initial investigations, including serum concentrations of luteinising hormone, prolactin and high-density lipoprotein/low-density lipoprotein fractions of cholesterol. Special investigations are not always required, but if patients fail to respond to minimally invasive treatments, such investigations may be necessary before other options can be explored. Colour Doppler imaging provides information about penile haemodynamics after maximal smooth-muscle relaxation has been induced with a vasoactive agent. Its aim is to distinguish arterial insufficiency and veno-occlusive dysfunction from other causes of erectile failure. Nocturnal penile tumescence and rigidity testing to evaluate the frequency, duration and rigidity of nocturnal erections is more of historical interest, and its contemporary use is largely limited to medicolegal assessment of erectile function.

**Impact of a diagnosis of ED**

It is increasingly recognised that a diagnosis of ED can have a profound impact on the patient’s and partner’s quality of life.12 ED can lead to withdrawal from intimacy, avoidance of all physical contact with a partner and an increase in emotional stress, which itself can perpetuate any psychogenic component to the ED. The condition can affect a man’s self-esteem and self-image, and lead to anxiety and hence depression. Treatment of ED has been shown to lead to resolution of depression and restoration of self-esteem, and thus improvement in quality of life.13

**Treatment options**

The treatment options for men with ED are now varied and effective when compared with those of 20 years ago. The selection from these various treatment options depends on several factors, such as severity of ED, underlying cause and patient and partner choice. The results of the few studies that have been performed indicate that the only lifestyle modification that may make a difference in ED incidence is continuation or initiation of physical activity. Midlife changes in lifestyle other than physical activity may not have a beneficial effect on ED because it is simply too late. Some studies have suggested that smoking cessation may improve erectile function, which other studies have refuted. In addition, use of some antihypertensive and lipid-lowering drugs may actually exacerbate ED.
Coronary artery disease and risk

It is well known that ED is associated with numerous risk factors for coronary artery disease (CAD), including lipid abnormalities, hypertension, smoking, diabetes, obesity and lack of physical activity. However, most physicians do not routinely ask cardiac patients about ED, and these patients often are reluctant or embarrassed to discuss it. In addition, there is a paucity of studies examining the effect of control of risk factors on ED once the ED has been diagnosed.

Accumulating evidence indicates that ED is a predictor of cardiovascular health. Men with proven vasculogenic ED or multiple vascular risk factors and suspected vasculogenic ED should be screened for silent myocardial ischaemia by treadmill stress electrocardiogram or computed tomography coronary angiography.

In men with CAD, fitness for renewed sexual activity should be assessed with an exercise stress test before initiating or resuming sexual activity. Ability to exercise up to 3–6 METs without evidence of myocardial ischaemia suggests a low risk of experiencing cardiac symptoms during sexual activity. In asymptomatic men, fitness for renewed sexual activity can be confirmed by tolerance of a simple exercise challenge of walking 1.5 km briskly on the level in 20 min (3–4 METs) or climbing two flights of stairs without limiting symptoms (6 METs) (Table 3).14

Psychosexual therapy

Psychosexual therapy for ED cannot be standardised because the source of anxiety varies between patients. Relationship difficulties, depression, guilt, problems with intimacy and lack of sexual experience may all increase anxiety and/or conflict, which may then manifest as ED. Psychosexual treatments range from simple sex education through improved partner communication to cognitive and behavioural therapy and are often combined with ED pharmacotherapy. Results of psychosexual therapy are relatively good in the short term, but long-term results are disappointing.15,16

Pharmacotherapy

Most patients suffering from ED will respond to the safe, effective oral pharmacological agents now available. These include the PDE5 inhibitors sildenafil, tadalafil and vardenafil. Other physical treatments, such as vacuum devices and intracavernosal drugs, are used 'on demand'; however, the rates of discontinuation with these treatment alternatives are high owing to side-effects, dislike of needles and unwillingness of the partner to participate.

A large proportion of patients has a combination of psychogenic and organic ED. Organic ED may be associated with progressively worsening performance anxiety, which further worsens erectile function. To treat these men holistically, the physician and psychotherapist may need to collaborate and combine counselling with a physical therapy, such as an oral pharmacological agent.

Pharmacological treatment

Oral pharmacological agents

PDE5 inhibitors are a breakthrough therapy in the treatment of ED (Table 4). The PDE5 inhibitors selectively inhibit PDE5 and increase the amount of cGMP available for smooth-muscle relaxation, inducing vasodilatation, increased corporal blood flow and erection.

Numerous studies have documented the efficacy, safety and tolerability of the potent, competitive on-demand PDE5 inhibitor drugs sildenafil (Viagra, Pfizer, Inc., New York, NY, USA), tadalafil (Cialis, Eli Lily and Company, Indianapolis, IN, USA) and vardenafil (Levitra, Bayer Schering, Pharma AG, Leverkusen, Germany), and daily dosing of tadalafil in the treatment of ED in a wide range of patients, including those with hypertension, diabetes, spinal cord injury, other concomitant medical conditions and in those patients taking a wide variety of concomitant medications.4,17,18 The overall efficacy for the different PDE5 inhibitors appears similar with 65–70% of men achieving completion of sexual intercourse. Efficacy is related to the extent and severity of ED, with significantly reduced efficacy demonstrated in patients with severe

Table 3 Guidelines for prescribing ED treatment in patients with cardiac disease

<table>
<thead>
<tr>
<th>Risk</th>
<th>Cardiac status</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>• Controlled hypertension</td>
<td>Manage in primary care</td>
</tr>
<tr>
<td></td>
<td>• Mild valvular disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mild stable angina</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Post-revascularisation</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>• Recent MI or cerebrovascular accident (6 weeks)</td>
<td>Specialised evaluation recommended</td>
</tr>
<tr>
<td></td>
<td>• Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Murmur of unknown cause</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Moderate stable angina</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>• Uncontrolled angina</td>
<td>Refer for cardiac opinion</td>
</tr>
<tr>
<td></td>
<td>• Uncontrolled hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Severe heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Recent MI or cerebrovascular accident (2 weeks)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High-risk arrhythmia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hypertrophic cardiomyopathy</td>
<td></td>
</tr>
</tbody>
</table>

ED, erectile dysfunction; MI, myocardial infarction.
vasculogenic ED, diabetic ED and post-radical prostatectomy ED. Data indicate that there are differences among sildenafil, tadalafil and vardenafil in pharmacokinetic properties, efficacy, potency, half-life and adverse effect profiles (Table 4). Food high in fat delays and reduces the absorption of sildenafil and vardenafil, but does not affect the rate or extent of absorption of tadalafil. The mean time to maximum plasma concentration of sildenafil and vardenafil is 1 h and for tadalafil is 2 h, while the half-lives of sildenafil and vardenafil are 4–5 h and that of tadalafil is 17.5 h.

Daily dosing with tadalafil (Cialis 2.5, 5 and 10 mg) results in efficacy and side-effect rates comparable with those of on-demand application of the highest doses of either tadalafil or other PDE 5 inhibitors, and can be considered first-line therapy, especially in men who engage in frequent intercourse or regard spontaneity of sexual intercourse as a key treatment goal.19 Daily dosing

Table 4 On-demand/daily phosphodiesterase type 5 (PDE5) inhibitors

<table>
<thead>
<tr>
<th>Action</th>
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<tr>
<td>Sexual arousal activates the nitric oxide/cGMP pathway. Inhibition of PDE5 results in increased corporal levels of cGMP, relaxation of penile vascular smooth muscle, increased corporal blood flow and augmented penile tumescence/erection.</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Drugs</td>
</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Sexual arousal is essential for a response</td>
<td>May occur as early as 20 min after on-demand administration</td>
</tr>
<tr>
<td>High fat meal limits speed and extent of absorption of sildenafil and vardenafil, but not tadalafil</td>
<td>Detumescence occurs immediately following ejaculation or cessation of sexual arousal</td>
</tr>
<tr>
<td>Duration of response following on-demand dosing</td>
<td></td>
</tr>
<tr>
<td>Sildenafil 4–6 h</td>
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</tr>
<tr>
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<td></td>
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<tr>
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</tr>
<tr>
<td>Assessment of drug selection</td>
<td>Choice of drug should be individualised to patient's needs</td>
</tr>
<tr>
<td>No ‘head-to-head’ comparative studies are available</td>
<td>The extended period of response to tadalafil may suit some patients</td>
</tr>
<tr>
<td>Daily dosing of tadalafil may offer some patients additional sexual spontaneity</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Metabolism</td>
</tr>
<tr>
<td>Rapidly absorbed after oral administration</td>
<td>Maximum plasma concentrations are reached within 30–120 min in the fasted state</td>
</tr>
<tr>
<td>Pharmacokinetics are dose-proportional over the recommended dose range</td>
<td>Extensively metabolised by CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Adverse effects are dose related and are usually mild to moderate severity</td>
</tr>
<tr>
<td>Most common are headache, facial and upper trunk flushing, dyspepsia, muscle/back ache and nasal congestion.</td>
<td>Transient alteration in colour vision may occur with sildenafil and vardenafil</td>
</tr>
<tr>
<td>No cases of priapism have been reported in routine clinical use</td>
<td></td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Concomitant use of potent cytochrome P450 3A4 inhibitors (e.g. erythromycin, ketoconazole, itraconazole and protease inhibitors) as well as the non-specific CYP inhibitor, cimetidine, is associated with increased plasma levels</td>
</tr>
<tr>
<td>Concomitant administration of CYP3A4 inducers, such as rifampin, will decrease plasma levels</td>
<td>Potentiation of the hypotensive effects of nitrates and administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated</td>
</tr>
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</tr>
<tr>
<td>cGMP, cyclic guanosine-3’5’-monophosphate; CYP, cytochrome P450.</td>
<td></td>
</tr>
</tbody>
</table>
may improve endothelial function and improve or restore erectile function. Salvage of on-demand tadalafil failures with daily or alternate day administered high-dose tadalafil (10–20 mg) has been reported but is limited by the relatively high cost of treatment.20

Treatment with PDE5 inhibitor drugs is generally well tolerated and the adverse effects reported are usually transient, mild to moderate in nature, dose dependent and often attenuate or disappear with continued use. The most commonly reported adverse effects are headache (11–16%), flushing (2–11%), dyspepsia (4–10%), muscle/back ache (0–4%) and nasal congestion (2–9%). In most instances, adverse effects are mild, are best managed symptomatically and will resolve with 4–6 weeks, but on occasions, cessation and/or a trial to a second PDE5 inhibitor drugs and another treatment may be indicated. Blindness due to non-arteritic anterior ischaemic optic neuropathy has been linked to the use of PDE5 inhibitors. Although a causal relationship has not been established, loss of vision or reduced vision, whether painful or painless, demands urgent patient assessment and immediate cessation of PDE5 inhibitor use.

PDE5 inhibitor drugs are contraindicated in patients taking aerosol, tablet or topical short- or long-acting organic nitrates, such as nitroglycerin or isosorbide dinitrate. PDE5 inhibitors have been shown to cause greater decreases in blood pressure in some patients on organic nitrates. There is currently no evidence of any direct deleterious effect on myocardium, and there is an increasing body of evidence to support the concept that PDE5 inhibitors improve endothelial function and, therefore, are likely to be cardioprotective.

**Intracavernosal injection (ICI) therapy**

Treatment with patient-administered ICI therapy using vasodilator drugs, such as alprostadil (Caverject Impulse, Pfizer) alone, or in combination with papaverine and phentolamine, which relax the arterial and trabecular smooth muscle, is an effective treatment for ED.21 ICI therapy can be used in most men with ED but is especially useful in men who fail to respond to oral pharmacological agents (Table 5).22

Alprostadil resulted in an erection of sufficient rigidity for sexual intercourse in 72.6% of men with ED.21 The principal side-effects of ICI of alprostadil are pain at the site of injection, which occurs in up to 30% of patients, and corporal fibrosis resulting in the development of penile nodules and curvature in 9–23.3% of mid- and long-term users. Priapism is a rare complication that can cause irreversible ischaemic damage to the corpora cavernosa with subsequent fibrotic damage and permanent loss of erectile function. Systemic side-effects are

<table>
<thead>
<tr>
<th>Table 5 Alprostadil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Action</strong></td>
</tr>
<tr>
<td>- Relaxation of trabecular smooth muscle and dilatation of cavernosal arteries, expansion of lacunae and entrapment of blood by compression of the drainage venules against the tunica albuginea</td>
</tr>
<tr>
<td>- Administered by direct intracorporal injection (Caverject, Pfizer Inc., New York, NY, USA)</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
</tr>
<tr>
<td>- 5–15 min of intracavernosal injection (ICI)</td>
</tr>
<tr>
<td>- Arousal is usually required to produce a maximal response.</td>
</tr>
<tr>
<td>- With correct dosing, detumescence should commence within 10–20 min of ejaculation, but a fully flaccid penis may not occur for a further 1–2 h.</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
</tr>
<tr>
<td>- Assess patient fitness for renewed sexual activity</td>
</tr>
<tr>
<td>- Administered 5–15 min before planned sexual activity</td>
</tr>
<tr>
<td>- Individualise dose by initial in-office physician supervised dosage titration using the lowest possible effective dose</td>
</tr>
<tr>
<td><strong>Caverject Impulse</strong></td>
</tr>
<tr>
<td>- 1 mL ampoules as Caverject Impulse 10 (10 mcg), Caverject Impulse 20 (20 mcg)</td>
</tr>
<tr>
<td>- Instruct patient in sterile injection technique, used needle disposal, management of prolonged erections</td>
</tr>
<tr>
<td>- Maximum frequency of use is no more than three times a week, with at least 24 h between each dose.</td>
</tr>
<tr>
<td>- Start with 5 mcg and titrate in 5 mcg increments to a maximum of 20 mcg</td>
</tr>
<tr>
<td>- Start with 1.25 mcg and titrate in 1.25 mcg increments in spinal cord injured (SCI) patients</td>
</tr>
<tr>
<td><strong>Management of prolonged erection</strong></td>
</tr>
<tr>
<td>- Use lowest possible effective dose</td>
</tr>
<tr>
<td>- If still rigid</td>
</tr>
<tr>
<td>- 2 h after administration – 120 mg pseudoephedrine</td>
</tr>
<tr>
<td>- 4 h after administration – 120 mg pseudoephedrine/walk briskly for 10–15 min</td>
</tr>
<tr>
<td>- 6 h after administration – contact treating doctor or hospital A&amp;E</td>
</tr>
<tr>
<td>- Some patients may require aspiration of corpora/irrigation with dilute vasoconstrictors/surgical drainage</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
</tr>
<tr>
<td>- Short duration of action and a brief plasma half-life</td>
</tr>
<tr>
<td>- 30% of the drug is metabolised within the corpora cavernosa and/or urethral mucosa and up to 80% after the first pass through the lung to inactive metabolites.</td>
</tr>
<tr>
<td><strong>Adverse effects</strong></td>
</tr>
<tr>
<td>- Mild penile pain (15–20%), priapism (0.25%) AND corporal fibrosis (5–10%) with long-term use</td>
</tr>
<tr>
<td>- Approximately 30% of users discontinue ICI each year</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
</tr>
<tr>
<td>- Systemic drug–drug interactions are unlikely due to low or undetectable levels of alprostadil in the peripheral venous circulation</td>
</tr>
</tbody>
</table>
uncommon (~1%), include dizziness, tachycardia and hypotension, and result from leakage of the drug into the circulation. Alprostadil has superior efficacy and reduced risk of priapism and intracorporal fibrosis compared with papaverine alone or in combination with phentolamine. As such, papaverine should be restricted to informed patients refractory to alprostadil.

Combination pharmacotherapy of alprostadil combined with other agents, such as papaverine and phentolamine, is effective in 91.6% of patients and appears effective as ‘salvage therapy’ in treating patients with severe vasculogenic ED.21

The self-injection technique should be taught by either the physician or the practice nurse. Relative contraindications to ICI therapy include anticoagulation, previous poor compliance and a history of priapism.

Vacuum constriction devices

The vacuum constriction device involves application of a vacuum to the penis in a vacuum cylinder causing tumescence and rigidity, which is sustained using a constricting ring at the base of the penis. The penile physiological changes differ from a normal erection in that trabecular smooth-muscle relaxation does not occur, and blood is simply trapped in both the intracorporal and extracorporal compartments of the penis distal to the constricting ring.

Vacuum constriction devices require a motivated patient and a cooperative partner. They are more popular in middle and old age group couples and are uncommon treatment choices in single younger men. Approximately 60–70% of men find the device straightforward. Satisfaction rates, both short and long term, vary considerably from as low as 27% to 68% short term, to as high as 69% with 2 years follow-up. Complications include petechiae, pain occurs at the site of the ring and ejaculatory changes, including pain on ejaculation and blocked ejaculation, numbness and pivoting of the penis at the base. Vacuum constriction devices are relatively contraindicated in men taking warfarin and in men with an increased risk of intravascular thrombosis due to myeloproliferative diseases and sickle-cell anaemia.

Surgical treatment

Surgical treatment of ED is usually reserved for patients in whom more conservative therapy has failed or for whom conservative therapy is contraindicated. Most of these patients will have significant arterial or venous disease, penile corpus cavernosum fibrosis or Peyronie disease, or will, by choice, prefer the prospect of a ‘one-off’ solution. While the outcome of surgical intervention may be more reliable in certain selected patients, the incidence of morbidity and complications is significantly greater than with medical treatment.

Penile prosthetic implants

Malleable or multicomponent inflatable penile implants are usually reserved for patients in whom more conservative therapy has failed and are associated with high satisfaction rates. Device failure and prosthetic infection are uncommon. Infection is the most problematic complication following surgery and often requires removal of the prosthesis, and either immediate replacement or staged reimplantation at a later stage.

ED in special populations

Peyronie’s disease

Peyronie’s disease is curvature of the penis due to fibrosis within the tunica albuginea. The affected corpora cavernosa cannot lengthen on erection, leading to curvature. The condition is most common in middle-aged men who are sexually active. Its exact aetiology remains unknown, but it may result from trauma and bleeding into the tunica, followed by activation of the inflammatory process and fibrosis. It is regarded as a disorder of wound healing, is associated with similar conditions such as Dupuytren’s contracture and Ledderhose disease, and may have an inherited basis.23

ED occurs in 30–40% of men with Peyronie disease. Although the mechanism of their ED is not clearly understood, most appear to have a vascular problem, such as arterial insufficiency where the fibrosis actually distorts the vessels or failure of the veno-occlusive mechanism. To a certain extent, treatment is determined by whether the patient has ED and Peyronie disease. If the patient has this combination, he may be best advised to undergo insertion of a penile implant, as surgical straightening of the penis alone is unlikely to overcome the ED. If penile curvature alone is the factor that precludes intercourse, medical or surgical treatment may be indicated. Medical treatment is limited to non-calcified plaques, curvatures less than 70 degrees, and is usually multimodal and may include antifibrotic agents, such as pentoxifylline (Trental, Paris, France) and intraplaque infiltrations with verapamil. Curvature can be surgically corrected by plaque excision and grafting or a Nesbit operation. This procedure involves shortening of the contralateral corpus cavernosum. Patients should be warned of the risks of penile shortening and onset of ED after surgery.
**Renal failure**
Chronic renal impairment is associated with a high incidence of ED, with the incidence increasing with the level of creatinine. ED is present in about 50% of patients by the time they require dialysis and is associated with anaemia, autonomic neuropathy, reduced testosterone levels with elevated prolactin, accelerated arterial disease, other drug therapies and psychological stress. Erythropoietin treatment and transplantation with normalisation of renal function often restore or improve the patient’s overall quality of life and erectile function.

**Pelvic surgery**
Damage to cavernous and other pelvic nerves following surgery to the rectum, bladder or prostate is often associated with erectile and/or ejaculatory dysfunction. Anatomic nerve-sparing surgical techniques minimise damage and reduce the risk of ED. Patients who undergo gastrointestinal surgery that results in an ileostomy or colostomy may suffer depression or loss of self-esteem, which may cause ED. Preliminary evidence suggests that the sooner pharmacological treatment is started after an operation, the more likely the patient is to regain normal erectile function.

**Penile injuries**
Blunt or penetrating injuries can cause a penile fracture, rupture of the tunica albuginea or neurovascular bundle damage, with resultant ED. Complete urethral disruption injuries from a pelvic fracture are almost universally associated with ED, often due to a combination of neurological and vascular impairment, which may be difficult to treat.

**Radiation therapy**
Pelvic radiation therapy, whether by external beam or brachytherapy with radioactive seeds inserted into the prostate, can produce ED. While ED rates immediately after external radiotherapy are low – less than 10% at 1 month and 12 months – they increase over time, with 33% of patients reporting ED at 36 months and a mean time to ED of 14.5 months.

**BPH with lower urinary tract symptoms (LUTS)**
Recent studies have shown a clear association between ED and BPH with LUTS. The association is independent of age, but the more severe the LUTS, the more severe the ED. Recent data have not only confirmed this association but also demonstrated a moderate effect of tadalafil on patients with LUTS.

**Conclusion**
ED is a common compliant and is often associated with a reduced quality of life for sufferer and partner. ED is associated with a variety of risk factors, including diabetes mellitus, hypertension, hyperlipidaemia and cigarette smoking. ED may be the first manifestation of generalised endothelial dysfunction and is a predictor of overall cardiovascular health and silent myocardial ischaemia. Treatment with ED pharmacotherapy alone or in combination with graded psychosexual therapy is effective in improving and/or restoring sexual function in most men.

**References**


McMahon CG. Comparison of the response to the intracavernosal injection of a combination of papaverine and phentolamine, prostaglandin E1 alone and a combination of all three in the management of impotence. *Int J Impotence Res* 1991; **3**: 133–42.

Australians’ knowledge and perceptions of direct-to-consumer personal genome testing

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Key words
predictive genetic testing, consumer health information, ethical issue, survey methodology.

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Abstract

Background: As direct-to-consumer personal genome testing (DTC-PGT) is increasingly available in Australia, knowledge of Australians’ perceptions and attitudes towards this technology is needed in order to assess the (potential) impact it might have on the Australian public and healthcare system.

Aims: To explore the knowledge and perceptions of DTC-PGT in an Australian sample.

Methods: An online survey asking about knowledge and perceptions of DTC-PGT, undertaken between October 2011 and April 2012, of 270 Australian residents. Results were analysed using SAS.

Results: Our study found limited consumer knowledge of, and interest in, pursuing DTC-PGT in Australia. Ninety-three per cent of respondents correctly identified DTC-PGT as available to consumers directly, but only 40% correctly identified its availability in Australia. When asked about the content and value of the information DTC-PGT provides, the majority of respondents identified that DTC-PGT could provide information about one’s health and/or ancestry (82% and 74%). Additionally, respondents indicated they believed this information to be equally important as non-genetic information about one’s ancestry and health.

Conclusion: While a minority of respondents expressed an intention to pursue DTC-PGT (27%), the majority of respondents, irrespective of whether they wished to pursue it or not, believed that genetic information was as important as non-genetic information in regards to their health and their ancestry. The value ascribed to genetic information suggests that genetics plays a role in people’s lives, and that further qualitative research could explore the ways in which people might use and understand the genetic information provided by DTC-PGT.

Introduction

Traditionally, people have accessed medical diagnostics and therapeutics through a health practitioner. However, the emergence of the Internet and other information technologies has profoundly changed this dynamic, and consumers are now able to access sophisticated biotechnologies without medical consent or advice. One of the most striking examples of this is direct-to-consumer personal genome testing (DTC-PGT). In this situation, consumers purchase an ‘at home’ DNA collection kit (usually a kit that collects a saliva sample) that they return to the company for testing. The company usually then emails a report of the test results to the consumer. This report may provide information about the consumer’s carrier status for several genetic conditions and risk estimates for common multifactorial diseases such as diabetes, heart disease, various cancers and Alzheimer disease. Testing may also provide information about ancestry, including an ancient ancestor migration report, an estimate of the likelihood that the consumer is from a particular ethnic group and a description of whether or not the consumer has ancestral genetic ties to certain historical figures. Since its introduction in 2007, DTC-PGT has functioned as a tool that individuals and groups (and families) can use as a means of accessing genetic information about themselves outside of the clinical setting.

The emergence and consumption of DTC-PGT can be explained, at least in part, by the increasing impact of genetic information in healthcare. It is also due to the increasing prominence of the notion of personalised medicine. Both of these factors emphasise the importance of genetic influences on and understandings of
health and illness, and of clinicians and consumers ‘knowing’ and acting upon this information. DTC-PGT, it is argued, promotes health by providing individuals with information they need to make informed healthcare decisions.1

There has, however, been considerable debate about the value of the information DTC-PGT provides, including how it is understood and/or used by consumers. Recent studies have explored characteristics and motivations of early DTC-PGT adopters outside Australia, including how consumers interpret and act on their risk reports,5 and whether health-related actions correspond appropriately to the genetic information received.1 Almost all of this research has been done in the United States, the most prominent market to date for DTC-PGT. While there are growing markets in China, Korea and India,6,4 cultural similarities between Australia and the United States make the former body of literature the most appropriate source of critical commentary. This research has also tended to focus on specific groups, including ‘early adopter’ populations,7,8 health and ‘high-tech’ company employees,9 social networkers,10 individuals who are affected or have a family member affected with a genetic condition,11–13 or individuals enrolled in particular studies to study the impact of genetic susceptibility testing.14 There are currently no data regarding the knowledge and perceptions of DTC-PGT in any Australian population.

We conducted an online survey between November 2011 and April 2012 to explore Australians’ knowledge and perceptions of DTC-PGT and their expressed interest in pursuing DTC-PGT for themselves.

Methods

Survey instrument and recruitment

An online survey consisting of 30 questions was designed to capture a sample of the Australian public’s knowledge and perceptions of DTC-PGT. The survey consisted of four sections. Section 1 requested demographic information relating to age, gender, country of birth, country of residence, level of general education and education around genetics. Section 2 asked respondents about their general knowledge of DTC-PGT, such as what DTC-PGT provides information about, who the test is available to, how the test can be obtained, how they heard about testing and whether they believed the test was legal or available in Australia. Section 3 asked respondents about their perceptions of the value information from DTC-PGT could provide. The final section asked those respondents who had undergone DTC-PGT about their experience of DTC-PGT, while non-consumers of DTC-PGT were asked if they were planning on pursuing DTC-PGT.

The survey was distributed through online mailing lists to a university student and staff population, through online networks to patient support groups for people living with genetic conditions, through a consumer health information website, a science and technology website, and through societies associated with genetic conditions in Australasia. The survey was launched in November 2011 and closed at the end of April 2012, and used the online survey tool peoplepulse.com.au. The survey took approximately 5 min to complete (a copy of the survey is available from the corresponding author). As a link to the survey was distributed through list serves and posted on a website for individuals to access, there were no tracking statistics attached to the survey link – meaning that the reported responses are of the number of surveys commenced and completed. The University of Sydney Human Research Ethics Committee approved this study and survey instrument (Approval and Reference #2012/2264).

Statistical analysis

Data were analysed using SAS 9.3 (SAS Institute, Inc., Cary, NC, USA) using the PROC SURVEYFREQ procedure to calculate frequencies based on the 270 responses included for analysis. Demographic factors (age, gender and education level) were tested in PROC SURVEYFREQ in tables using adjusted Pearson’s chi-square analysis at a $P \leq 0.05$ level of significance. Summary statistics for relevant variables are reported using PROC SURVEYFREQ and are reported with 95% confidence intervals (CIs).

Results

Demographics

Overall, 402 surveys were commenced, of which 282 were completed. Of these, 270 were completed by individuals who resided in Australia and were included in the analysis.

Table 1 summarises the demographic data. Respondents were categorised into three age groups according to characteristics that we felt may be relevant to awareness and uptake of DTC-PGT. The first age group (18–31 years) was chosen to include a population demographic that is generally familiar with genetic concepts (e.g. through school science education) and with several of the media platforms used to promote DTC-PGT (e.g. social media and online blogs). The second age category (32–45 years) was chosen to encompass potential consumers with permanent jobs, with disposable incomes and who are still in their reproductive years. This group also
includes those who have completed their post-secondary or postgraduate education. The final age category (46 and up) was chosen on the grounds that it was likely to include people who may be less interested in the implications of genetic information for their own reproductive choices but who might still have an interest in some of the information DTC-PGT provides about future health and ancestry.

Expressed intention to pursue DTC-PGT

When asked if they planned on pursuing DTC-PGT, 73.0% (95% CI 72.7–73.2%) indicated that they were not, while 27.0% (95% CI 26.8–27.3%) said they were intending to or were currently having DTC-PGT done. No demographic variables – including age, gender or education – were predictive of an interest in pursuing DTC-PGT.

Knowledge about DTC-PGT and its availability

In section 2 of the survey, all questions were ‘forced’ answers – without an option of ‘I don’t know’. When asked what type of testing could be done using DTC-PGT, most responded that DTC-PGT could be used for health testing (82%; 95% CI 81.2–81.8%) and ancestry testing (74.4%; 95% CI 74.1–74.8%). This is consistent with respondents’ expectations of the information provided by DTC-PGT, with most indicating that DTC-PGT would provide information about one’s health (particularly one’s future health) and ancestry (Table 2).

The vast majority (93.3%; 95% CI 93.2–93.5%) of respondents correctly indicated that DTC-PGT was available to anyone (as it is now), with 75.2% (95% CI 74.9–75.5%) (correctly) indicating that consumers themselves could purchase a DTC-PGT. It should be noted that in the introduction to the survey, respondents were provided with a definition of direct-to-consumer. Fewer respondents – 24.4% (95% CI 24.1–24.8%) – incorrectly believed that a doctor must request DTC-PGT. Of those surveyed, 40.4% (95% CI 40.0–40.7%) correctly thought it was available in Australia (as it is now), while 53.3% (95% CI 53.0–53.7%) were unsure. In addition, 54.8% (95% CI 54.5–55.2%) of respondents did not know if DTC-PGT was ‘legal’ in Australia, while 43% (95% CI 42.6–43.3%) correctly believed that it was (and remains so). At the time of the survey, Australians were able to access DTC-PGT online through providers located overseas; there was also one Australian company offering these tests.

Perceived value of the information provided by DTC-PGT

Respondents were asked how they rated the value of the information that DTC-PGT could provide in terms of its importance to the individual. Respondents were asked to indicate whether these data had medical, personal or familial importance (or any combination of these), or whether the information was simply ‘interesting’. Respondents could choose multiple answers. The frequency count is expressed as a percentage of the total number of responses, not the total number of respondents. CI, confidence interval; DTC-PGT, direct-to-consumer personal genome testing.

Table 1 Demographic information frequency summary

<table>
<thead>
<tr>
<th>Age</th>
<th>Percentage of respondents (n = 270 (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–31</td>
<td>55.9% (55.6–56.3%)</td>
</tr>
<tr>
<td>32–45</td>
<td>20.7% (20.4–21.0%)</td>
</tr>
<tr>
<td>46 and up</td>
<td>23.3% (23.0–23.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Percentage of respondents (n = 270 (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>27.0% (26.8–27.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>72.9% (72.7–73.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education</th>
<th>Percentage of respondents (n = 270 (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary education or Less</td>
<td>21.4% (21.2–21.8%)</td>
</tr>
<tr>
<td>Post-secondary education and higher</td>
<td>78.5% (78.2–78.8%)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

Table 2 What information DTC-PGT provides to consumers: survey responses to the question, ‘DTC-PGT provides genetic information to consumers. What do you think this information could tell you about?’

<table>
<thead>
<tr>
<th>What the information from DTC-PGT could tell you about</th>
<th>Frequency of responses (n = 1174 (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your future health</td>
<td>89.3 (89.0–89.5)</td>
</tr>
<tr>
<td>Your ancestry</td>
<td>84.4 (84.2–84.7)</td>
</tr>
<tr>
<td>Your current state of health</td>
<td>64.1 (63.7–64.4)</td>
</tr>
<tr>
<td>Your family</td>
<td>58.9 (58.5–59.2)</td>
</tr>
<tr>
<td>Your future children</td>
<td>48.5 (48.1–48.9)</td>
</tr>
<tr>
<td>Your physical appearance</td>
<td>35.6 (35.2–35.9)</td>
</tr>
<tr>
<td>Your children</td>
<td>35.2 (34.8–35.3)</td>
</tr>
<tr>
<td>Your personality</td>
<td>18.9 (18.6–19.2)</td>
</tr>
</tbody>
</table>

Respondents could select more than one answer. The frequency count is expressed as a percentage of the total number of responses not the total number of respondents. CI, confidence interval; DTC-PGT, direct-to-consumer personal genome testing.
important for themselves (44.8%; 95% CI 44.4–45.2%) and their family (38.9%; 95% CI 38.5–39.2%). Respondents were also asked which type of information they believed was more important in determining their health: (i) their genetically predicted health status or (ii) their health history and current health status. The majority of respondents selected that they were equally important (62.2%; 95% CI 61.9–62.6%). Likewise, respondents were asked which type of information they believed was more important in determining their ancestry – their known family ancestry and stories or their genetically determined ancestry. Again, the majority of respondents also selected that they were equally important (53.7%; 95% CI 53.3–54.1%).

### Discussion

This study provides the first empirical account of knowledge and perceptions of DTC-PGT in an Australian context. Several findings from this survey are particularly interesting. First, the results of this study suggest limited knowledge of, and interest in, pursuing DTC-PGT. Second, when asked about the content and value of the information DTC-PGT provides, the majority of respondents identified that DTC-PGT could provide information about one’s health and/or ancestry, and appeared to value this information as much as non-genetic information about one’s ancestry or their current/future health.

Only 40% of respondents correctly identified that DTC-PGT is available in Australia (as it is now), with the majority of respondents (54.8%) being unaware whether DTC-PGT was ‘legal’. DTC-PGT was and remains legal. But while respondents appeared uncertain about the availability or legality of DTC-PGT, respondents knew they were (as they currently are) able to access this technology independently from healthcare providers. The fact that respondents appeared to have a limited awareness of DTC-PGT is unsurprising, as at the time this survey was distributed (November 2011 to April 2012), there was no direct-to-consumer advertising in the Australian market. However, Australians accessing the Internet could be exposed to online advertisements for these services. Prior to and during the time in which the survey was conducted, there was also discussion of other types of DTC-PGT in popular culture, such as the television show, ‘Who do you think you are’, newspaper articles about these tests and what they could offer to consumers, and radio reports. While only 27% of the survey sample expressed an interest in pursuing DTC-PGT, the finding that more than half of respondents indicated that they believed the tests to be informative, relevant and valuable suggests the potential for greater uptake. The relational aspect of genetic information between family members who are genetically related raises the potential for DTC-PGT to inform and have an impact on an individual and perhaps their family. This impact can be in regards to their future health and/or their accepted narratives regarding their ancestry. As genetic information may be understood and acted upon by individuals, families and groups in different ways, it is imperative that the benefits and limits of this information are understood, and appropriate options are available, so people are able to act upon this information in a meaningful way.

There are two limitations to this study that caution against overinterpretation of these data. First, the data are from an online survey sent out through email lists associated with a university student and staff network, through genetic disease/disorder awareness societies around Australia, a science and technology website, and through a health consumer website. As a result, there is potential for selection bias to younger, educated individuals and towards individuals’ knowledgeable about genetics, genetic disorders/diseases and genetic screening/testing programmes. Indeed, our data tend to support this observation – with the largest proportion of respondents being younger (55.9% were aged 18–32) and respondents with a post-secondary or higher education (78.5%). This is an overrepresentation, as the 2011 Australian census data found only 24% of the population to be individuals between 18 and 34 years of age, with 26% of those within this group attending a post-secondary institution. Second, the overall sample size is small. To be representative of the Australian population, a larger cross-section of the public would need to be sampled. Despite the limitations to this study, our data provide a preliminary view of knowledge and perceptions of the Australian public towards DTC-PGT.
**Conclusion**

As the cost of sequencing continues to fall and the understanding of the information this technology provides advances, the next step in genetic technologies – whole genome sequencing – is likely to become a feature of both clinical care and the health marketplace. Until such time that whole genome sequencing is a routine part of clinical care, it is likely that Australians who wish to know more about their genetics (but who do not have a clinical ‘indication’) will seek this information through DTC-PGT services. At this stage, however, it is unclear what the clinical, public health and social impact of DTC-PGT will be. Although (only) 27% of the respondents to our study expressed an intention to pursue testing (a very large number of people if cautiously generalised to the Australian community), it is particularly noteworthy that the majority of respondents, irrespective of whether or not they wished to pursue DTC-PGT, indicated that they believed the information provided by DTC-PGT was as important as one’s ancestral stories, medical history and current health status. This apparent privileging of genetic information in understanding one’s self and one’s future health suggests that genetics has already deeply infiltrated our culture. Further quantitative research with a nationally representative sample is needed to explore who might be interested in pursuing these tests, while qualitative research could explore the ways in which people might use and understand the genetic information provided by DTC-PGT.

**References**

17 Dow S. Getting up close and personal. *Sydney Morning Herald* 2008; **20**.
Epidemiology of biopsy-proven giant cell arteritis in South Australia

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Key words
giant cell arteritis, epidemiology, vasculitis, incidence.

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Abstract

Background/Aim: To determine the epidemiology and clinical features of biopsy-proven giant cell arteritis (GCA) in South Australia (SA).

Methods: Patients with biopsy-proven GCA were identified from pathology reports of temporal artery biopsies at SA Pathology laboratories, from 1 January 1992, to 31 July 2011. Epidemiological data were collected through patient questionnaires and standardised case note reviews. Incidence was estimated using Australian Bureau of Statistics population data for SA. Seasonality was analysed by Cosinor analysis, and time-to-event analysis was performed for the duration of steroid use.

Results: There were 314 cases of biopsy-proven GCA (72% female). The mean age at diagnosis of GCA was 78 years (interquartile range 72–82). The estimated population incidence for people over 50 was 3.2 per 100 000 person years. The female : male incidence ratio was 2.3 (P < 0.001), and incidence increased with each age decade. There was evidence of seasonal variation (P = 0.015), with higher rates observed in the summer months.

Clinical data were available for 163 patients (68% female, median age 78 years). The most common presenting clinical features were temporal headache (74%), visual disturbance (68.4%), jaw claudication (59.3%) and symptoms of polymyalgia rheumatica (56%). The median initial steroid dose was 60 mg, with median duration of steroid use 4.5 years. Corticosteroid side-effects were common, affecting 89%, with 34% reporting five or more.

Conclusions: This is the first epidemiological study of Australian biopsy-proven GCA patients. Age at onset and gender associations were similar to other Western populations. There was a high burden of steroid use in these patients.

Introduction

Giant cell arteritis (GCA), also known as temporal arteritis, is a systemic vasculitis which primarily affects medium to large extra-cranial arteries of the head and neck but can, more rarely, affect the aorta and arteries in the upper and lower limbs.1 GCA is characterised by ischaemic symptoms, such as temporal headaches, scalp tenderness, jaw/upper limb claudication, stroke, visual disturbance and permanent visual loss. Other common inflammatory symptoms include low grade fever, malaise, weight loss and anorexia.1 Rapid diagnosis and treatment are essential as high-dose corticosteroid treatment can prevent further visual loss or stroke.2 Recently, use of low-dose aspirin has been advocated as retrospective studies have demonstrated it to be associated with decreased rates of visual loss and reduced cranial ischaemic complications.3 Due to the high doses of corticosteroid required, the majority of patients will experience at least one side-effect during the long-term treatment course.4

GCA primarily affects people aged over 50 years, with incidence rates increasing with advancing age and peaking around the age of 80.1 It is more common in females than in males, with the ratio in some populations reported to be up to fivefold higher.3–8 GCA is most commonly seen in Caucasians with the highest incidence reported in Scandinavian countries and equally high-incidence rates reported in Olmsted County Minnesota, a population with a strong Scandinavian genetic background.9 Incidence is
lower in southern European countries,\textsuperscript{10,11} while GCA is reportedly rare in Asian, Hispanic, Middle Eastern and African populations.\textsuperscript{12} Studies of the incidence and clinical features of biopsy-proven GCA have not previously been undertaken in Australia.

The aim of this study was to determine epidemiological and clinical features of biopsy-proven GCA patients in South Australia.

**Methods**

**Ascertainment of biopsy-proven giant cell arteritis cases**

All pathology reports of patients who underwent temporal artery biopsy were identified from pathology laboratories at the three major South Australian adult teaching hospitals (The Queen Elizabeth Hospital, Royal Adelaide Hospital and Flinders Medical Centre). These laboratories process approximately 85% of biopsy specimens from both public and private hospitals in South Australia.


All pathology reports of temporal artery biopsies during this time period were reviewed and patients with biopsy-proven GCA were identified. Patients were defined as having biopsy-proven GCA if this diagnosis was made by the reviewing pathologist on the diagnostic report.

**South Australian GCA Registry**

Further clinical and epidemiological data were collected from 163 biopsy-proven South Australian GCA patients in the form of questionnaires and case note reviews. These patients were recruited through the South Australian Giant Cell Arteritis Registry, established in 2009. Patients with biopsy-proven GCA were identified as outlined above. Letters were first sent to each patient’s treating doctor (general practitioner or specialist) asking permission to contact that patient. If permission was given, the patient was then contacted by letter and by telephone to explain the study. If patients were willing to participate, they were sent a patient information sheet, consent form and a questionnaire regarding the presentation, symptoms and management of their disease. Patients were also provided with a reply paid envelope in which to return their signed consent form and completed questionnaire. Once consented, a standardised case note review was performed, and all data were recorded, in conjunction with the patient’s questionnaire, in a Microsoft Access database. The registry contains information on each individual’s demographics (such as gender, date of birth, age at onset and ethnicity), clinical features (such as presenting symptoms and inflammatory marker levels), treatments, side-effects and concurrent medical conditions.

This study has ethics approval at The Queen Elizabeth Hospital, The Royal Adelaide Hospital and Flinders Medical Centre/Repatriation General Hospital. Ethics committee approval includes permission to access case notes of deceased patients without obtaining consent from next of kin.

**Statistical analysis**

Epidemiological data were analysed using the freely available statistical analysis software ‘R’ (version R 2.15.1, Vienna, Austria)\textsuperscript{13} and the software plug-in ‘Rcmdr’\textsuperscript{14}. Wilcoxon nonparametric tests were used to compare continuous measurements between two groups. Other tests performed include Chi-squared or logistic regression for contingency tables. A Poisson regression was performed to calculate incidence rates per 100 000 person years (by age and gender) using the South Australian population data for relevant years as an offset.\textsuperscript{15} A Cosinar analysis was performed to calculate seasonal trends in incidence using the ‘R’ software plug-in ‘season’.\textsuperscript{16,17} This analysis fits a cosine curve to the monthly data available for the years 1991 to July 2011. Steroid duration was calculated by performing a time-to-event analysis using the ‘R’ software plug-in ‘survival’ (Therneau T, New York, New York, USA). Data were considered complete if the patient completed their corticosteroid treatment course. Data were considered incomplete for duration of corticosteroid analysis if patients died prior to cessation of corticosteroid treatment or if they were still taking corticosteroids at last follow up. A time-to-event analysis was performed to investigate the duration of steroid treatment following GCA diagnosis.

**Results**

**Summary of all South Australian biopsy proven GCA patients**

There was a total of 314 positive temporal artery biopsies between 1991 and July 2011. The median age at biopsy was 78 years (interquartile range 72–82 years) (Fig. 1).

The incidence of biopsy-proven GCA was estimated at 3.2 (95% confidence interval (CI) 2.8, 3.6) per 100 000 person years. Incidence rates in the population per 5-year period from 1991 to July 2011 were relatively stable (Fig. 2A). Females were approximately twice as likely as males to have biopsy-proven GCA with an observed incidence ratio of 2.3 (95% CI 1.8, 2.9, \( P < 0.001 \), Fig. 2B).
The incidence of GCA increased with advancing age. The lowest incidence rate of 0.2 (95% CI 0.1, 0.4) was observed in the youngest age group (50–59 years) while the highest incidence of 10.1 (95% CI 8.4, 12.2) was observed in the 80+ age group (Fig. 2C). A significant yearly seasonal trend in GCA incidence was identified ($P = 0.015$), with the largest number of positive biopsies diagnosed in the warmer months December and January (Fig. 3). However, the amplitude of the cosine curve, which reflects the maximum seasonal difference in incidence, was relatively small.

**Comparison between GCA patients on the registry and those not on the registry**

Of the 314 biopsy proven GCA patients diagnosed between 1991 and July 2011, 151 have not been added on to the registry (Fig. 4). Of these, 73 patients (48%) could not be contacted, 46 (31%) did not give consent, and the remaining 32 (21%) are yet to be contacted and may be added to the registry in the future (Fig. 4). There were no significant differences between patients participating and those not participating in the registry in terms of gender ($P = 0.11$) or age at onset ($P = 0.33$).

**Summary information for biopsy proven GCA patients on the registry**

All patients were aged over 50 years, and 68.1% of patients were female. All but one patient was Caucasian (one patient Asian). All patients met American College of Rheumatology Classification criteria for GCA (27). A summary of presenting symptoms and lifestyle factors for GCA patients on the registry is reported in Table 1 ($n = 163$). The most common presenting symptoms were new onset temporal headaches, visual disturbance, jaw claudication and scalp tenderness. Blindness affected 37%
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with monocular blindness affecting the majority (93%). Nearly a quarter had a preceding polymyalgia rheumatica (PMR) diagnosis (Table 1). Temporal artery biopsies were performed by ophthalmologists (65.1%), vascular surgeons (21.7%) and others (13.2%).

Laboratory data from within ±30 days of the temporal artery biopsy were recorded. High ESR was observed in 86.9% of patients while high C-reactive protein was observed in 75.6% of patients. Other markers of acute inflammation were present, such as anaemia (30.7%), thrombocytosis (42.6%) and leucocytosis (30.7%).

Males were more likely than females to exhibit symptoms of visual disturbance ($P = 0.047$) and weight loss ($P = 0.009$) while a younger age at biopsy was associated with more systemic systems, such as fatigue ($P = 0.0014$), fever ($P = 0.014$) and weight loss ($P = 0.05$). There were no associations found between either previously diagnosed PMR or PMR symptoms at the time of diagnosis and age at biopsy ($P = 0.092$). However, there was an association observed with both fatigue ($P = 0.02$) and weight loss ($P = 0.04$).

**Comorbidities and concomitant medications**

Comorbidities were very common at diagnosis and included hypertension (66.9%), ischaemic heart disease (35.8%), cancer (34.9%), hypercholesterolaemia (30.9%), chronic lung disease (26.5%), asthma (17.9%) and diabetes (17.3%).

The most common concomitant medications taken by patients on the registry ($n = 163$) were medications for osteoporosis (67.7%), aspirin (46.0%), warfarin (11.9%) and cholesterol lowering agents (35.9%, Table 2). Of the 14.7% of patients taking steroid-sparing agents, the majority were taking methotrexate (89.5%), with one patient taking azathioprine.
Corticosteroid use, duration and side-effects

The most common starting dose of corticosteroid dose was 40–60 mg daily (median 60 mg daily) with some starting doses up to 80–100 mg daily recorded (n = 116). All but one patient received oral prednisolone. In addition to oral prednisolone, 37.9% also received intravenous corticosteroid treatment. Those who presented with blindness (P < 0.001) or visual disturbance (P = 0.002) were more likely to receive intravenous corticosteroid treatment. The median duration, representing the time at which 50% of patients remained on corticosteroids, was 4.5 years (n = 86, Fig. 5).

Comprehensive corticosteroid side-effect data were available for 122 GCA patients (Table 3). The most commonly reported steroid side-effects were bruising (44.6%), cataracts (41.2%) and proximal weakness (33.3%).

As expected, the majority of patients reported experiencing corticosteroid side-effects with only 10.7% of patients reporting no side-effects. The majority of patients reported 1–2 side-effects (38.2%), 16.4% of patients reported 3–4, while 34.4% of patients reported experiencing 5 or more.

Discussion

A comprehensive study of biopsy-proven GCA patients has not previously been undertaken in Australia. Here, a population-based study of the epidemiological, demographic and clinical features of patients with biopsy-proven GCA in South Australia is reported for the first time. The overall annual incidence rate was found to be lower than those reported for other Caucasian populations, such as those in Europe,6,10,11,18–20 the United Kingdom,4 United States9 and New Zealand.3 The reported incidence rate in this study may however be an underes-

Table 2  Concomitant medications taken by patients on the giant cell arteritis (GCA) registry

<table>
<thead>
<tr>
<th>Medication</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td></td>
</tr>
<tr>
<td>Previous or current prednisolone treatment</td>
<td>142/143 (99.3)</td>
</tr>
<tr>
<td>Intravenous corticosteroid</td>
<td>44/116 (37.9)</td>
</tr>
<tr>
<td>Other medications</td>
<td>148/153 (96.7)</td>
</tr>
<tr>
<td>Anti-osteoporosis treatments</td>
<td>92/136 (67.6)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>64/139 (46.0)</td>
</tr>
<tr>
<td>Cholesterol lowering agents</td>
<td>47/131 (35.8)</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
<td>19/129 (14.7)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>17/19 (89.5)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1/19 (5.3)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>1/19 (5.3)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>16/134 (11.9)</td>
</tr>
</tbody>
</table>

Table 3  Summary of corticosteroid side-effects experienced by patients, ranked in order of frequency

<table>
<thead>
<tr>
<th>Corticosteroid side-effect</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruising</td>
<td>54/121 (44.6)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>54/128 (42.2)</td>
</tr>
<tr>
<td>Proximal weakness</td>
<td>40/120 (33.3)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>33/120 (27.5)</td>
</tr>
<tr>
<td>Oedema</td>
<td>33/123 (26.8)</td>
</tr>
<tr>
<td>Depression</td>
<td>33/125 (26.4)</td>
</tr>
<tr>
<td>Moon facies</td>
<td>32/122 (26.2)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>30/121 (24.8)</td>
</tr>
<tr>
<td>Gastrointestinal disturbance</td>
<td>30/122 (24.6)</td>
</tr>
<tr>
<td>Fragility fracture</td>
<td>28/128 (21.9)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>24/122 (19.6)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>23/122 (18.8)</td>
</tr>
<tr>
<td>Mood disturbance</td>
<td>23/125 (18.4)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>12/117 (10.3)</td>
</tr>
<tr>
<td>High blood sugar</td>
<td>10/122 (8.2)</td>
</tr>
<tr>
<td>Oral thrush</td>
<td>10/122 (8.2)</td>
</tr>
<tr>
<td>New onset diabetes</td>
<td>8/111 (7.2)</td>
</tr>
<tr>
<td>Vaginal thrush</td>
<td>4/86 (4.7)</td>
</tr>
</tbody>
</table>
Epidemiology of giant cell arteritis in SA

We observed seasonal variation in incidence of GCA with increased incidence in summer months. Previous studies have also reported seasonal/cyclic trends in incidence rates, although no consistent pattern has emerged. Seasonal peaks in incidence have also been reported during the summer months in the United Kingdom, in late spring/early summer in Israel, but in late winter/autumn in Sweden and during January and May in Scotland. Other studies have also reported cyclical patterns in GCA incidence, which we did not observe. A study from Olmstead County Minnesota, conducted over a 50-year period from 1950–1999, reported five peaks in incidence occurring approximately every 7 years and lasting up to 3 years each. A recent study from Otago, New Zealand found that over a 10-year period, two peaks in incidence occurred approximately 5 years apart.

This seasonal or cyclic variation in incidence may potentially indicate an infectious trigger for GCA, although no such infectious agent has been identified. A Danish study, spanning a 12-year period from 1982–1994, reported associations between peaks in GCA incidence and coincident epidemics of *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and Parvovirus B19 in multiple counties. However, other studies have failed to find any associations between infectious agents and variation in GCA incidence rates.

A cluster of associations was observed between age at biopsy and presenting systemic symptoms, such as fatigue, fever and weight loss. This suggests that patients with a younger age at onset have a more systemic disease. Similarly, fatigue and weight loss were also associated with patients who had a pre-existing PMR diagnosis or PMR symptoms at biopsy. A pre-existing diagnosis of PMR was observed in 26% of GCA patients. A total of 56% of GCA patients reported either a preceding PMR diagnosis or PMR symptoms at biopsy. This is consistent with existing literature that states that between 40–60% of GCA patients will experience symptoms of PMR and that younger patients are more likely to present with systemic symptoms and PMR.

The prevalence of monocular blindness of 37% was significantly higher than that noted in a recent study from New Zealand (10/70; 14.3%). Other recent studies have reported varying incidence of monocular blindness. A study from an Italian cohort reported 19.1% of patients experienced either partial or total visual loss, while a study from Spain observed irreversible visual loss in 12.5% of patients, and a study from Japan reported complete visual loss in 6.5% of patients. This may be related to the retrospective nature of the data collection, in which not all patients agreed to join the GCA Registry and those who had suffered a significant sequelae from GCA, such as blindness, may have been more likely to agree to join the registry. The incidence of biopsy-proven GCA in SA was lower than observed in New Zealand, suggesting that treating doctors in SA may be less likely to arrange temporal artery biopsies. This raises the issue of whether treating doctors in SA may have been more likely to request a temporal artery biopsy if visual disturbance or loss was present at presentation, leading to higher prevalence of this clinical feature in this GCA registry data. Future GCA studies in SA will be prospective which will overcome this problem.

Currently, corticosteroid treatment is the only effective treatment currently available for GCA despite many common and predictable side-effects. The most common side-effects reported in this study were bruising, cataracts and proximal weakness with only 10% of patients reportedly free of steroid side-effects, indicating the very high burden of corticosteroid related side-effects in the GCA population. This burden is also higher than a previous study which reported that at least 50% of GCA patients would experience one or more side-effect as a result of the corticosteroid treatment.

The most common initial corticosteroid dose given to South Australian GCA patients was 40–60 mg/day (median 60 mg daily). This is comparable to the optimal initial dose of 40–60 mg/day recommended in the British Society for Rheumatology guidelines for GCA management. Most symptoms respond rapidly to corticosteroid treatment, and once they resolve, the dose can gradually begin to be tapered. In this cohort, 50% of patients were still receiving corticosteroid treatment 4.5 years after their biopsy date. Other literature reports the mean corticosteroid treatment course to be between 1 and 2 years. The reason for the long duration of corticosteroid treatment in this South Australian cohort is unclear and requires further investigation as the burden of corticosteroid adverse events is considered to be related to duration of use. The long duration of corticosteroid...
use is also relevant in this cohort given the older age of the patients and high frequency of comorbidities, such as osteoporosis, hypercholesterolaemia, ischaemic heart disease and hypertension, which may be exacerbated by the use of corticosteroids.

The high burden of corticosteroid use in this GCA cohort underlines the need for alternative, steroid-sparing, therapeutic strategies. Steroid-sparing agents, like methotrexate or azathioprine, are used to enable a more rapid tapering of the corticosteroid dose. A recent meta-analysis of methotrexate in GCA revealed that it reduces the number of relapses in GCA and reduces the cumulative corticosteroid dose. Clinical trials of other agents to reduce corticosteroid use in GCA, such as infliximab and azathioprine, have not been successful. Randomised controlled trials of biologic agents, such as anti-IL6 agents, are currently underway.

However, despite the serious consequences of GCA and the required high-dose corticosteroid therapy, the mortality rate is generally reported to be equal to the general population. A recent study of mortality in South Australian biopsy-proven GCA patients reported no significant differences in mortality between GCA patients and the general South Australian population, after adjusting for age and gender. However, the study did conclude that GCA patients were at a higher risk of death due to infection, especially early on in the treatment course. This is likely to be related to the high-dose corticosteroid treatment used initially and the attendant impairment of immunological defence.

As with any clinical research, there is the difficulty of recruiting and consenting patients. In the case of GCA, this is perhaps even more challenging due to the late age at onset of the disease. GCA patients have an average at onset of 78 years and as this study was conducted retrospectively, many of the patients were very elderly at the time of contact or were deceased. Despite being the most common vasculitis affecting the elderly, GCA is also relatively rare, with only 3.2 cases per 100 000 person years in the South Australian population. Many patients have other intervening illnesses, as a result of age, which further adds to the difficulty of recruitment. Prospective recruitment of GCA patients at the time of diagnosis remains the optimum solution for capturing comprehensive clinical and laboratory data.

Conclusion

Epidemiological and clinical data for a previously unstudied GCA population has been reported here for the first time. It is clear that many factors play a role in the onset of GCA from genetic to pathogenic and environmental factors. The striking increase in susceptibility to this disease with advancing age suggests that an age-related or degenerative change within a tissue constituent may render elderly persons vulnerable to this inflammatory disease, possibly though an immunological mechanism.

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Inflammatory bowel disease cancer surveillance in a tertiary referral hospital: attitudes and practice
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Key words
inflammatory bowel disease, dysplasia, surveillance, colitis, colorectal cancer.

Abstract

Background: Physician adherence to guidelines for colorectal cancer (CRC) surveillance in inflammatory bowel disease (IBD) is often poor. This may lead to adverse patient outcomes and excess endoscopic workload.

Aims: To assess the attitudes and practice of IBD specialists in a tertiary centre towards colonoscopic surveillance.

Methods: First, a questionnaire evaluating attitudes and approach to CRC surveillance was issued to 36 clinicians at one tertiary referral hospital. Second, a retrospective audit of IBD surveillance colonoscopy practice over a 2-year period was performed.

Results: Questionnaire response rate was 97%. Sixty-nine per cent of respondents were aware of, and used, Australian guidelines. Surveillance was undertaken by all clinicians in patients with extensive colitis, 83% in patients with left-sided colitis and 51% in patients with proctitis. Seventy-six per cent used chromoendoscopy, and 47% took 10 to 20 random biopsies. Colectomy was considered appropriate in 0% for unifocal low-grade dysplasia, 35% for multifocal low-grade dysplasia and 83% for high-grade dysplasia. Sixty-six per cent would remove elevated dysplastic lesions endoscopically. The audit identified 103 surveillance colonoscopies in 81 patients. Chromoendoscopy was used in 21% of cases, and the median number of random biopsies was 13. Sixty-two per cent of colonoscopies were performed outside the guidelines in relation to colonoscopic frequency. Following colonoscopy, an appropriate recommendation for subsequent surveillance was documented in 40% of cases.

Conclusions: Knowledge and practice of CRC surveillance in IBD vary among specialist clinicians and often deviate from guidelines. Many clinicians perform surveillance earlier and more frequently than recommended. These findings have implications for patient outcomes and workload.

Introduction

Patients with ulcerative colitis (UC) and Crohn disease (CD) have an increased risk of developing colorectal cancer (CRC) compared with the general population.1–3 Several factors increase the risk of CRC in patients with inflammatory bowel disease (IBD), including disease duration4 and extent,5 severity of inflammation,6,7 concomitant primary sclerosing cholangitis (PSC)8 and a family history of CRC.9

The most important known predictive factor for the development of CRC in IBD is the presence of mucosal dysplasia.10 Colonoscopic surveillance aims to detect dysplasia prior to the development of invasive malignancy and to detect cancer at an early stage. While no randomised study has been conducted to demonstrate the efficacy or cost-effectiveness of colonoscopic surveillance in patients with IBD, various case–control studies have shown that surveillance in UC is associated with earlier cancer diagnosis, reduced overall death rates and improved cancer-related survival.11–17

Guidelines from various groups have endorsed surveillance colonoscopy in patients with IBD.18–21 Contemporary guidelines have incorporated new developments in cancer surveillance, placing greater emphasis on clinical and endoscopic risk factors to stratify the intensity of surveillance. The use of improved endoscopic technology...
and technique, including chromoendoscopy, has improved diagnostic efficacy.\textsuperscript{22–24} Certain dysplastic lesions are now considered amenable to endoscopic removal rather than requiring surgery.\textsuperscript{25,26}

Colonoscopic surveillance for cancer and dysplasia can be time consuming, expensive and invasive, all factors that may lead to poor patient and physician compliance. Difficulties in detecting and interpreting dysplasia, particularly in the setting of active inflammation, may result in diagnostic errors or uncertainty. Clinicians’ lack of understanding and adherence to surveillance guidelines may reduce the efficacy of these programmes. Previous studies have suggested that adherence to existing guidelines varies widely among clinicians and is often inconsistent.\textsuperscript{27–30} Recent revised guidelines from the UK, USA and Australia have increased emphasis on stratifying patients according to risk and have provided for the use of new endoscopic diagnostic technologies and treatments. We aimed to determine if specialists in a centre with a major focus on IBD are familiar with these developments and guidelines, and determine how they apply them in practice.

We surveyed all gastroenterologists and colorectal surgeons at St Vincent’s Hospital, Melbourne, a tertiary referral centre for IBD, to assess their approach to CRC surveillance in patients with IBD. A confidential questionnaire was administered to all gastroenterologists, colorectal surgeons and their specialist trainees at St Vincent’s Hospital, Melbourne, to determine their understanding of, and adherence to, Australian CRC surveillance guidelines published by the National Health and Medical Research Council in December 2011.\textsuperscript{18} We also reviewed the files of 81 consecutive IBD patients undergoing cancer surveillance colonoscopy between November 2010 and December 2012. The aims of this study were to compare self-reported practice with actual practice, and compare current practice with local Australian guidelines.

Methods

Questionnaire

A confidential questionnaire was administered to all gastroenterologists, colorectal surgeons and their specialist trainees at St Vincent’s Hospital, Melbourne, to assess their approach to CRC surveillance in patients with IBD. The questionnaire contained 21 multiple-choice questions with options for open responses (Appendix 1). Questions covered topics including attitudes to surveillance, starting surveillance, intervals between colonoscopies, colonoscopy and biopsy practice, and management of dysplasia.

Audit

A retrospective search of the endoscopy software database was performed to identify IBD patients undergoing surveillance colonoscopy at our institution between November 2010 and December 2012. Data concerning patient demographics, disease-related factors, risk factors for CRC, colonoscopy practice and management of dysplasia were extracted from the medical records and endoscopy reports. Timing of the current colonoscopy as well as recommendations for the subsequent colonoscopy were assessed and compared with Australian guidelines.

Results

Questionnaire

Questionnaires were distributed to 36 clinicians, and 35 completed responses were received: 18 from gastroenterologists, 10 from advanced gastroenterology trainees and 7 from colorectal surgeons and their trainees.

Attitudes to surveillance colonoscopy in IBD

All respondents would perform surveillance colonoscopy for patients with UC, while 86\% would perform surveillance colonoscopy for patients with CD. Sixty-nine\% of respondents stated that they were aware of the Australian guidelines and that they use them regularly. Twenty-two\% reported using other guidelines while three respondents would not use any guidelines.

Timing and frequency of surveillance

Participants were asked if and when they would initiate surveillance colonoscopy for patients with proctitis, left-sided colitis and extensive colitis (Fig. 1). Forty per cent of respondents would never initiate surveillance colonoscopy in patients with proctitis, whereas 34\% and 23\% would start 8–10 or 10–15 years after disease onset respectively. Most participants would initiate surveillance for left-sided colitis (57\% of respondents) and extensive colitis (71\% of respondents) 8–10 years after onset of disease. Clinicians were asked about the frequency of colonoscopic surveillance in patients with quiescent proctitis, left-sided colitis or extensive colitis in the absence of any additional risk factors for CRC (Fig. 2). Fifty-one\% per cent would continue surveillance in patients with proctitis, some as frequently as every 2 years. Eighty-three\% per cent would enrol patients with left-sided colitis in a surveillance programme while all respondents would do so for patients with extensive colitis. Most would recommend colonoscopy every 2 or 3 years in these settings.

Colonoscopy practice

While 76\% of respondents reported that they used chromoendoscopy, only 27\% of respondents would use it...
frequently or always (Fig. 3a). All respondents would take targeted biopsies of suspicious lesions, but the number of additional random biopsies varied: 21% would take less than 10 random biopsies while most (47%) would take 10–20 random biopsies. When directly asked how often they would take 2–4 random biopsies per colonic segment, 80% reported doing this always or frequently (Fig. 3b).

Management of dysplasia

Participants were asked how they would manage the findings (confirmed by two pathologists) of unifocal low-grade dysplasia (LGD), multifocal LGD or high-grade dysplasia (HGD) detected on random biopsies from flat colonic mucosa (Fig. 4). No respondents would recommend colectomy for patients with unifocal LGD, opting instead for more intensive colonoscopic surveillance. The management of multifocal LGD was more diverse with 35% of respondents stating that they would refer for colectomy and the remainder preferring to intensify surveillance. Most respondents (83%) would recommend colectomy for patients with HGD. When asked how they would manage the finding of an elevated dysplastic lesion within an area of inflammation, 66% of respondents would attempt to remove the lesion endoscopically, 14%...
would refer for colectomy and the remainder would intensify surveillance.

Audit of practice

The endoscopy database contained 103 CRC surveillance colonoscopies performed on 81 IBD patients between November 2010 and December 2012. Patient characteristics are shown in Table 1.

Colonoscopic practice

Caecal intubation was achieved in 95% of colonoscopies. Both disease activity and extent were documented in 81% of reports. Chromoendoscopy was used in 21% of cases. The median number of random biopsies taken per colonoscopy was 13.

Colonoscopy findings and management

Of 1299 random biopsies, one case of multifocal LGD was identified. This patient was advised to have a repeat colonoscopy with chromoendoscopy and biopsies 3 months later. Two cases of indefinite dysplasia were found. Both patients remain under colonoscopic surveillance.

In seven patients, adenomatous lesions were identified in non-inflamed areas of colon. All lesions were removed endoscopically, and none contained advanced neoplastic changes. These lesions were all thought to be sporadic adenomas, and these patients remain under surveillance. In two patients, elevated lesions were detected within areas of inflammation. In both cases, histology revealed tubulovillous adenomas with LGD. The first patient was advised to undergo repeat colonoscopy in 3 months after successful polypectomy. The second patient with multifocal dysplasia was advised to undergo surgery.

One cancer was found during surveillance. A 56-year-old man with a 31-year history of steroid-dependent, chronically active, extensive UC and PSC was found to have active colitis with a raised, indistinct, sessile polyp in the descending colon. Biopsies revealed an invasive, poorly differentiated adenocarcinoma. There was also evidence of multifocal LGD and HGD on biopsies taken from areas of irregular nodular mucosa. Colonoscopy 17 months previously had shown active pancolitis with no evidence of dysplasia. The patient has declined surgical treatment.

Timing of colonoscopy and further recommendations

To determine whether practice at our institution was already in line with recommendations ultimately
published in 2011 and whether the guidelines impacted on practice, we compared timing of the current colonoscopy as well as the recommendation for subsequent colonoscopy (where available) with Australian guidelines. We defined a deviation in time of 20% or less as being in keeping with the guidelines. Deviations of 21–50% and >50% were defined as minor and major deviations respectively. Of the 103 colonoscopies performed during the study period, 38% were performed at a time that was in keeping with the Australian guidelines (Fig. 5a). Of the 57 colonoscopies that were performed outside of the guidelines, 51% were performed sooner than recommended.

Recommendations for future surveillance colonoscopies were documented in only 63% of cases. Of these, 61% were in keeping with the Australian guidelines (Fig. 5b). Thus, a recommendation in line with Australian guidelines was documented in only 40% of all colonoscopies. Of the recommendations that deviated from the guidelines, 70% would result in colonoscopy being performed earlier than necessary.

Fifty-six per cent of recommendations made before publication were already in accordance with the Australian guidelines. This increased to 70% after publication ($P = 0.18$; not significant).

**Discussion**

This study describes both the attitudes and practice of gastroenterologists and colorectal surgeons at a single tertiary hospital with regard to CRC surveillance in patients with IBD. The questionnaire response rate of 97% together with an audit of clinical practice ensures that this study provides a true reflection of the state of CRC surveillance at our institution. To our knowledge, this is the first study to compare self-reported CRC surveillance with actual clinical practice. We found that while clinical practice was broadly in keeping with self-reported practice, there still appears to be significant variation among clinicians as well as deviation from published guidelines.

Australian guidelines for CRC surveillance were updated in December 2011 and now contain a chapter on CRC surveillance in IBD. Although our survey was conducted almost 12 months later, only two-thirds of respondents were aware of these guidelines and used them regularly.

This study looked at three critical components of CRC surveillance, including the timing of surveillance colonoscopy, colonoscopic practice and management of dysplasia.

### Timing of surveillance colonoscopy

While all respondents stated that they would perform surveillance colonoscopy in patients with UC, 14% would not undertake surveillance in patients with Crohn colitis. The risk of CRC in patients with Crohn colitis appears similar to that in patients with UC, and recent guidelines advocate surveillance for these patients. In the absence of other risk factors, patients with proctitis or distal colitis are at low risk of developing CRC, but screening colonoscopy is usually advocated 8–10 years after disease onset to ensure that there has been no proximal extension of colitis, a practice undertaken by only one-third of survey respondents. As long as inflammation has never extended proximal to the sigmoid colon, these patients do not require ongoing surveillance, yet just over half of the surveyed clinicians in our study recommended regular colonoscopies for patients with proctitis. According to Australian guidelines, patients with quiescent extensive UC and no other risk factors...
should begin surveillance 8–10 years after disease onset. While most respondents would begin surveillance after 8–10 years, 51% would opt for 2-yearly surveillance in these patients.

The validity of questionnaires may be limited by recall bias, as respondents may provide answers they feel are correct rather than representative of their actual practice. To complement our survey, we conducted an audit on 103 consecutive surveillance colonoscopies performed over a 2-year period. Thirty-seven per cent of colonoscopies were performed at a time that was in keeping with the Australian guidelines. A little over half of the 57 colonoscopies performed outside the Australian guidelines were performed sooner than recommended. Clinician recommendations for further surveillance after colonoscopy were in keeping with the Australian guidelines in 61% of colonoscopies; 70% of the remainder would have resulted in subsequent colonoscopy being performed sooner than necessary.

Overall, in our study, surveillance colonoscopy was often performed more frequently than required and, in some cases, in patients in whom the risk of CRC is too low to justify surveillance at all.

**Colonoscopic practice**

An effective surveillance programme not only relies on optimal timing and frequency of colonoscopic examination, but also the optimisation of colonoscopic practice to maximise diagnostic yield. It has been estimated that 33 biopsies are required to detect dysplasia with 90% probability, but even then, only a tiny proportion of total surface area of the colon is sampled, and foci of dysplasia can easily be missed. Forty-seven per cent of participants in our questionnaire stated that they would take between 10 and 20 random biopsies with two respondents taking more than 30 biopsies. Our audit revealed that the mean number of random biopsies taken per colonoscopy was 13, lower than that reported in other studies. While this approach may help document the extent of histologically active disease, it remains insufficient to reliably detect dysplasia if present. Recent evidence suggests that most dysplastic lesions are visible at colonoscopy, allowing biopsies to be targeted to suspicious lesions. Use of newer endoscopic techniques, such as chromoendoscopy, further increases the diagnostic yield. The role of random biopsies therefore remains controversial, with some experts believing that they should be abandoned and that standard practice should incorporate the use of chromoendoscopy and targeted biopsies of visibly abnormal mucosa. Others advocate taking of two to four random biopsies from flat mucosa in each colonic segment. While 76% of survey respondents reported using chromoendoscopy, only 21% of surveillance colonoscopies performed during the study period utilised chromoendoscopy. Eighty per cent of participants stated they take two to four random biopsies per colonic segment ‘always’ or ‘frequently’.

**Management of dysplasia**

The finding of HGD in flat mucosa is highly predictive of established or imminent carcinoma, and most guidelines recommend colectomy in this situation. In our survey, most respondents would advocate colectomy for patients with HGD. Management of LGD in flat mucosa is more controversial, mainly due to uncertainty about its value in predicting established or future CRC, with rates of progression to advanced neoplasia varying among studies. This uncertainty is reflected in surveillance guidelines, which suggest that decisions regarding colectomy versus continued surveillance in the setting of flat LGD need to be made on an individual basis. It is generally agreed that the risk of CRC is higher in patients with multifocal than unifocal LGD. In our study, all respondents would continue, and most likely intensify, surveillance for patients with unifocal LGD, while the finding of multifocal LGD would prompt 35% of respondents to refer for colectomy. These results are in keeping with responses obtained in similar questionnaires performed in the UK and USA, but referral rates for colectomy were lower than those reported in other studies from New Zealand and the USA.

The majority of respondents (66%) in our study felt that endoscopic removal of an elevated dysplastic lesion in an area of inflammation was appropriate. Only 14% would refer for colectomy in this situation, unlike the colectomy referral rates ranging from 58% to 98% reported in other studies. The low colectomy referral rate in our study may reflect a more recent paradigm shift, highlighted in the British, US and Australian guidelines, which suggests that elevated lesions, even in areas of inflammation, can be removed endoscopically without the need for surgery, provided that the lesion is removed in its entirety and that there is no dysplasia in biopsies taken from surrounding flat mucosa or elsewhere in the colon.

The yield from random biopsies was low in our audit, with only one case of LGD and two cases of indefinite dysplasia identified from 1299 random biopsies taken from flat mucosa. Elevated dysplastic lesions were identified in nine patients, and most were removed endoscopically in keeping with responses obtained from the questionnaire and in line with published guidelines. One CRC was detected during surveillance. The patient had extensive, chronically active colitis and PSC, but...
colonoscopy 17 months earlier had not detected any dysplastic lesion. This case highlights the need for vigilance in patients at high risk for CRC.

We recognise that this study has several limitations. It was performed at a single tertiary referral centre with an expertise in IBD and interventional endoscopy, attracting a more complex patient load that may not be reflective of patient populations at other institutions or in the community. The audit was performed retrospectively and only included patients attending for surveillance colonoscopy during the study period. Part of the audit was conducted prior to publication of the Australian guidelines, and this may have led to a greater discordance between survey results and observed practice. Although the questionnaire was limited to a single institution, it included clinicians with a range of interests, experience and expertise, and did not focus purely on gastroenterologists with a subspecialty interest in IBD.

Overall, we found that gastroenterologists and surgeons at our institution offer CRC surveillance for most patients with IBD, but adherence to published guidelines is variable and there appears to be room for improvement. Similar conclusions were drawn from questionnaires performed in the Netherlands, New Zealand and the UK, and a retrospective review of colonoscopic practice in Canada. Many clinicians tend to err on the side of caution, often performing surveillance earlier and more frequently than recommended. Despite this study being performed at a single centre, we still found significant variation in attitudes and practices of clinicians, reflecting the difficulties doctors have in understanding, remembering and adhering to guidelines.

Conclusion

Guidelines from the major gastroenterological societies now appear consistent with their recommendations. They all place a major emphasis on risk stratification to determine ideal surveillance intervals on an individual basis, and incorporation of better endoscopic technique and new technologies to improve diagnostic efficacy. With better awareness, acceptance of and eventually adherence to guidelines, CRC surveillance practice could be optimised with the potential benefits of shorter endoscopy waiting lists, reduced patient risk, better patient compliance and improved cost-effectiveness. Ultimately, these benefits may also result in better outcomes with regard to diagnostic efficacy, patient management and survival.

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Cancer surveillance in IBD


46 O dze R D, F arraye F A, H echt J L, H ornick J L. Long-term follow-up after polypectomy treatment for adenoma-like dysplastic lesions in...
Appendix 1

Questionnaire

1. Do you recommend surveillance colonoscopies for detection of dysplasia/cancer in your patients with ulcerative colitis?
   a) No
   b) Yes

2. Do you recommend surveillance colonoscopies for detection of dysplasia/cancer in your patients with Crohn’s Disease?
   a) No
   b) Yes

3. Are you aware of the most recent Australian ‘Clinical Practice Guidelines for Surveillance Colonoscopy’ published in 2011, which includes specific recommendations regarding colonoscopic surveillance in inflammatory bowel disease?
   a) No
   b) Yes

4. Do you follow any of the published guidelines for colonoscopic surveillance of IBD patients?
   a) No
   b) Yes, Australian guidelines (NHMRC/Cancer Council Australia)
   c) Yes, US guidelines (American Gastroenterology Association)
   d) Yes, British guidelines (British Society of Gastroenterology)
   e) Other guidelines (please specify) ..........................

5. When would you initiate surveillance colonoscopy for a patient with proctitis and no other risk factors for colorectal cancer?
   a) Never
   b) Less than 8 years after onset of disease
   c) 8–10 years after onset of disease
   d) 10–15 years after onset of disease
   e) Other (please specify) ..........................

6. When would you initiate surveillance colonoscopy for a patient with left-sided colitis (colitis distal to the splenic flexure) and no other risk factors for colorectal cancer?
   a) Never
   b) Less than 8 years after onset of disease
   c) 8–10 years after onset of disease

7. When would you initiate surveillance colonoscopy for a patient with extensive colitis (extending proximal to the splenic flexure) and no other risk factors for colorectal cancer?
   a) Never
   b) Less than 8 years after onset of disease
   c) 8–10 years after onset of disease
   d) 10–15 years after onset of disease
   e) Other (please specify) ..........................

8. How frequently would you recommend that patients with quiescent proctitis undergo surveillance colonoscopy in the absence of any dysplastic lesions or other risk factors (i.e. PSC, FHx of CRC)?
   a) No surveillance
   b) Yearly
   c) Every 2 years
   d) Every 3 years
   e) Every 4–5 years
   f) Other (please specify) ..........................

9. How frequently would you recommend that patients with quiescent left-sided colitis (distal to the splenic flexure) undergo surveillance colonoscopy in the absence of any dysplastic lesions or other risk factors (i.e. PSC, FHx of CRC)?
   a) No surveillance
   b) Yearly
   c) Every 2 years
   d) Every 3 years
   e) Every 4–5 years
   f) Other (please specify) ..........................

10. How frequently would you recommend that patients with quiescent extensive colitis (proximal to the splenic flexure) undergo surveillance colonoscopy in the absence of any dysplastic lesions or other risk factors (i.e. PSC, FHx of CRC)?
    a) No surveillance
    b) Yearly
    c) Every 2 years
    d) Every 3 years
    e) Every 4–5 years
    f) Other (please specify) ..........................
11. Which of the following factors would influence your screening and surveillance protocol for patients with IBD (can choose more than one option)?
   a) Age of patient
   b) Extent of colitis
   c) Duration of disease
   d) Family history of colorectal cancer in first degree relative <50 years of age
   e) Family history of colorectal cancer in first degree relative >50 years of age
   f) Diagnosis of primary sclerosing cholangitis
   g) Presence of structural changes within the colon (e.g. pseudopolyps, stricture, tubular colon)
   h) History of adenomatous polyps
   i) History of dysplasia found on biopsies from flat mucosa
   j) Other (please specify) ...........................................

12. What is your approach to taking biopsies when performing surveillance colonoscopy in IBD patients?
   a) No biopsies
   b) Targeted biopsies of lesions only (no random biopsies)
   c) Targeted biopsies of lesions and <10 random biopsies
   d) Targeted biopsies of lesions and 10–20 random biopsies
   e) Targeted biopsies of lesions and 21–30 random biopsies
   f) Targeted biopsies of lesions and >30 random biopsies

13. How frequently do you take 2–4 random biopsies from flat mucosa in each colonic segment?
   a) Always (100% of surveillance colonoscopies)
   b) Frequently (~75% of surveillance colonoscopies)
   c) Sometimes (~50% of surveillance colonoscopies)
   d) Infrequently (~25% of surveillance colonoscopies)
   e) Never (0% of surveillance colonoscopies)

14. How frequently do you use chromoendoscopy when performing surveillance colonoscopy in patients with IBD?
   a) Always (100% of surveillance colonoscopies)
   b) Frequently (~75% of surveillance colonoscopies)
   c) Sometimes (~50% of surveillance colonoscopies)
   d) Infrequently (~25% of surveillance colonoscopies)
   e) Never (0% of surveillance colonoscopies)

15. What is your approach to the finding of unifocal low-grade dysplasia (confirmed by two pathologists) on a random biopsy from flat mucosa?
   a) Repeat colonoscopy <6 months
   b) Repeat colonoscopy 6–12 months

16. What is your approach to the finding of multifocal low-grade dysplasia (confirmed by two pathologists) on random biopsies from flat mucosa?
   a) Repeat colonoscopy <6 months
   b) Repeat colonoscopy 6–12 months
   c) Repeat colonoscopy in 12 months
   d) Refer for colectomy
   e) Other (please specify) ...........................................

17. What is your approach to the finding of high-grade dysplasia (confirmed by two pathologists) on a random biopsy from flat mucosa?
   a) Repeat colonoscopy <6 months
   b) Repeat colonoscopy 6–12 months
   c) Repeat colonoscopy in 12 months
   d) Refer for colectomy
   e) Other (please specify) ...........................................

18. What is your approach to the finding of an elevated dysplastic lesion within an area of inflammation?
   a) Repeat colonoscopy <6 months
   b) Repeat colonoscopy 6–12 months
   c) Repeat colonoscopy in 12 months
   d) Remove lesion by polypectomy or endoscopic mucosal resection
   e) Refer for colectomy
   f) Other (please specify) ...........................................

19. When do you usually make a recommendation regarding the need for and timing of the next surveillance colonoscopy?
   a) At or directly after colonoscopy
   b) At the first subsequent clinical visit
   c) Shortly before next surveillance colonoscopy due
   d) Other (please specify) ...........................................

20. Which one of the following best applies to you?
   a) Gastroenterologist
   b) Gastroenterology trainee (fellows/registrar s)
   c) Surgeon/surgical trainee

21. Do you have a particular subspecialty interest in IBD?
   a) No
   b) Yes
Direct ultrasound localisation for pleural aspiration: translating evidence into action

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pleural effusion, ultrasonography, paracentesis, decision tree, pleural disease.

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Abstract
Background: There is strong evidence that direct ultrasound localisation for pleural aspiration reduces complications, but this practice is not universal in Australia and New Zealand.
Aims: To describe the current utilisation and logistical barriers to the use of direct ultrasound localisation for pleural aspiration by respiratory physicians from Australia and New Zealand, and to determine the cost benefits of procuring equipment and training resources in chest ultrasound.
Methods: We surveyed all adult respiratory physician members of the Thoracic Society of Australia and New Zealand regarding their use of direct ultrasound localisation for pleural aspiration. We performed a cost-benefit analysis for acquiring bedside ultrasound equipment and estimated the capacity of available ultrasound training.
Results: One hundred and forty-six of 275 respiratory physicians responded (53% response). One-third (33.6%) of respondents do not undertake direct ultrasound localisation. Lack of training/expertise (44.6%) and lack of access to ultrasound equipment (41%) were the most frequently reported barriers to performing direct ultrasound localisation. An average delay of 2 or more days to obtain an ultrasound performed in radiology was reported in 42.7% of respondents. Decision-tree analysis demonstrated that clinician-performed direct ultrasound localisation for pleural aspiration is cost-beneficial, with recovery of initial capital expenditure within 6 months. Ultrasound training infrastructure is already available to up-skill all respiratory physicians within 2 years and is cost-neutral.
Conclusion: Many respiratory physicians have not adopted direct ultrasound localisation for pleural aspiration because they lack equipment and expertise. However, purchase of ultrasound equipment is cost-beneficial, and there is already sufficient capacity to deliver accredited ultrasound training through existing services.

Introduction
Pleural aspiration performed for the diagnosis of pleural effusion has historically been guided by clinical localisation1 with its attendant risks of pneumothorax and solid organ puncture.2,4 However, ultrasound localisation increases safety,3 and complications are reduced irrespective of the size of the pleural effusion.7

Not all ultrasound guidance is beneficial. Direct ultrasound localisation performed immediately before the procedure is most effective in contrast with ultrasound-guided marking performed prior to aspiration at a remote location (so called ‘X marks the spot’), which does not reduce pneumothorax risk.5 Previously, direct ultrasound localisation could only be performed by radiology staff, but we now know that trained clinicians can achieve comparable efficacy and safety.9 Bedside chest sonography at one institution was demonstrated to reduce aspiration-related pneumothorax rates eightfold.3

In line with evidence, clinical practice guidelines recommend the use of direct ultrasound localisation for all pleural procedures for pleural fluid.1,10 We sought to determine whether clinical practice in our region conformed to guidelines because there is a global pattern of health systems failing to use evidence optimally.11

Our study addresses a series of three questions. First, what is the gap between evidence and practice?12 Second, what are the barriers in implementing best practice? Third, are these problems soluble?
Methods

In order to evaluate the gap between evidence and practice, all adult respiratory physician members of the Thoracic Society of Australia and New Zealand (TSANZ) were invited to respond to an online survey between November 2011 and January 2012. We presented a clinical scenario (Fig. 1) to gauge if respondents used direct ultrasound localisation for pleural aspiration in their current clinical practice, whether performed by a clinician or radiologist. Based on survey responses, we determined our respondents' ideal method of obtaining the aspirate if there were no constraints to their practice. We also determined access to direct ultrasound localisation either by radiologists or by clinicians.

To ascertain the perceived barriers that prevent the adoption of direct ultrasound localisation, we also asked respondents to report what constraints they felt were present. Response per cent for each question was based on the number of respondents answering that individual question. Results were analysed using Graphpad (Graphpad Software, Inc., San Diego, CA, USA) using Fisher's exact test with a significance level of 0.05.

We considered potential solutions to the problems identified by assessing expertise constraints. First, we determined the annual capacity of accredited courses in chest ultrasound across Australasia from the website of the Australasian Society of Ultrasound in Medicine (ASUM). We then used the guidelines provided by ASUM in order to estimate training capacity based on a minimum of 10 clinically indicated ultrasound procedures and five pleural aspirations (or tube insertions) performed under supervision. Procedure volumes were then estimated using data obtained through an audit of the number of pleural ultrasound procedures performed by members of the Department of Respiratory Medicine at the Royal Melbourne Hospital over 12 months. We used this to estimate the number of clinicians who could be trained across hospitals (deemed likely to have significant volumes of chest ultrasound procedures) throughout Australia and New Zealand.

We also evaluated downstream costs of investigating pleural effusion with or without bedside chest ultrasound by applying decision analysis (TreeAge Pro 2009, Excel module. TreeAge Software, Inc., Williamstown, MA, USA). Unit cost estimates, in Australian dollars, were based on hospital costs at the Royal Melbourne Hospital in the year 2010/2011. Cost per bed day was $562 (Y Sok-Wee, pers. comm., 2010); conservative management of pneumothorax, $540; and management requiring intercostal catheter, $1413. Input parameters for the decision tree are recorded in Table 1.

Key assumptions in the analysis were:
• Clinical and bedside aspiration was performed with no delay.
• Identical staff costs.
• Failed clinical aspiration was followed by radiology performed aspiration.
• Each arm of our model concluded with successful aspiration.
• Pathology costs, downstream costs of care and long-term outcomes were the same in all arms, regardless of the method by which diagnosis was achieved.

Results

Of 275 physicians practising adult respiratory medicine, we received 146 responses (response rate 53%) (Table 2). The majority practised in Australia (86.9%) or New Zealand (11.9%) with 0.3% from the southern region of New Zealand. The majority practised in general practice (82.4%) and rural hospitals (60.2%).

Figure 1 Clinical scenario. A 65-year-old male ex-smoker presents with cough and has dullness to percussion and reduced breath sounds at the right lung base. A plain chest radiograph performed (see below) demonstrating a moderate right-sided pleural effusion.

If pleural aspiration was required and the patient was currently under your care, which of the following statements best describes how this would occur:

1. Aspiration AT THE BEDSIDE with clinical localisation (percussion)
2. Aspiration AT THE BEDSIDE with direct US localisation (performed by you or a colleague)
3. Aspiration AT THE BEDSIDE after US localisation IN RADIOLOGY
4. Aspiration performed IN RADIOLOGY by a radiologist after US localisation IN RADIOLOGY
5. Thoracoscopic procedure performed by a physician or thoracic surgeon
6. I do not manage pleural effusions in my practice

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Zealand (12%), were employed by the public health system (84.9%) and worked in metropolitan areas (89.0%). Almost all (98.6%) of the respondents managed pleural effusions.

In response to the clinical scenario (Fig. 1), 66.4% of physicians reported their patients receive direct ultrasound localisation: 39.0% at the bedside and 27.4% in the radiology department (Fig. 2).

Of concern, over one-third (33.6%) of physicians do not currently perform ultrasound guidance for pleural aspiration: 13.7% would utilise a previously marked site in radiology ('X marks the spot'), while 19.9% would use

Table 1  Input parameters for decision tree analysis comparing clinician-performed direct ultrasound localisation, radiologist-performed direct ultrasound localisation and clinical localisation for pleural aspiration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clinically guided centesis</th>
<th>Clinician performed direct-ultrasound centesis</th>
<th>Radiologist performed direct-ultrasound centesis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay until procedure</td>
<td>Nil</td>
<td>Nil</td>
<td>≥3 days (23%)</td>
<td>Current study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 days (40%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 day (50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nil (8%)</td>
<td></td>
</tr>
<tr>
<td>Failed centesis</td>
<td>18%</td>
<td>0%</td>
<td>0%</td>
<td>Rahman et al9, Grogan et al25</td>
</tr>
<tr>
<td>Pneumothorax not requiring tube drainage</td>
<td>9%</td>
<td>1%</td>
<td>1%</td>
<td>Duncan et al9, Rahman et al9, Grogan et al25</td>
</tr>
<tr>
<td>Pneumothorax requiring tube drainage</td>
<td>3%</td>
<td>0.5%</td>
<td>0.5%</td>
<td>Rahman et al9, Grogan et al25</td>
</tr>
</tbody>
</table>

Table 2  Respondents by predominant site of practice

<table>
<thead>
<tr>
<th>Respiratory physicians</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 275)</td>
<td>146 (53% response rate)</td>
</tr>
<tr>
<td>Tertiary public hospital</td>
<td>96 (65.8%)</td>
</tr>
<tr>
<td>Non-tertiary public hospital</td>
<td>12 (8.2%)</td>
</tr>
<tr>
<td>Metropolitan private practice</td>
<td>22 (15.1%)</td>
</tr>
<tr>
<td>Rural/regional</td>
<td>16 (11.0%)</td>
</tr>
<tr>
<td>Not practising</td>
<td>2 (1.4%)</td>
</tr>
</tbody>
</table>

In response to the clinical scenario (Fig. 1), 66.4% of physicians reported their patients receive direct ultrasound localisation: 39.0% at the bedside and 27.4% in the radiology department (Fig. 2).

Of concern, over one-third (33.6%) of physicians do not currently perform ultrasound guidance for pleural aspiration: 13.7% would utilise a previously marked site in radiology ('X marks the spot'), while 19.9% would use
only clinical localisation. Without constraints, 85.1% of respondents would use direct ultrasound localisation. Interestingly, in this situation, most respondents preferred clinician-performed direct ultrasound localisation, with those opting for radiologist-performed direct ultrasound localisation dropping from 27.4% to 6.8% even though this was an acceptable guideline-recommended practice. The remainder of respondents would still proceed with either clinical localisation (12.8%) or remote ultrasound localisation (2.1%) (Fig. 2).

Figure 3 demonstrates that 42.7% of respondents reported a delay of 2 or more days to obtain an ultrasound in radiology. Almost half (48.6%) of all respondents reported no access to portable bedside ultrasound at their primary place of work (Fig. 4). Physicians at tertiary centres have greatest access, followed in order by those at non-tertiary metropolitan centres, rural practitioners and private practitioners. The difference in access between tertiary centre physicians and private practitioners is considerable and statistically significant (57.3% vs 18.2%, \( P = 0.0009 \)).

Seventy-five per cent of respondents reported constraints to accessing bedside thoracic ultrasound, and these are detailed in Figure 5. Forty-one per cent reported the lack of equipment, and 22.3% reported being constrained by its cost (Fig. 5). Lack of training or expertise in ultrasound was a reported constraint for 44.6% of respondents (Fig. 5). In fact, although approximately half the respondents reported some form of training, only 4.1% had completed both a formal course and a period of supervised practice until deemed competent (Fig. 6). These are the minimum recommended standards for independent practice in chest ultrasound.\(^{18,19} \) The 23.3% report lack of time as a constraint (Fig. 5), and this was most pressing among physicians in metropolitan private practice, affecting 45.5% in this group compared with 19.4% among their public hospital counterparts (\( P = 0.003 \)). Only 7.8% of respondents volunteered constraints other than the options we offered (Fig. 4).

Decision tree analysis demonstrated that clinician-performed direct ultrasound localisation for pleural aspiration, at base-case analysis, achieves a saving of AU$812 per patient compared with radiology-performed direct ultrasound localisation and a saving of AU$203 per patient compared with clinical localisation (Fig. S1). Longer radiology delays increase the degree of cost-benefit; a mean delay of 1 or 2 days results in a cost-benefit of AU$562 or AU$1236 per patient, respectively, in favour of clinician-performed direct ultrasound localisation. One-way sensi-
tivity analysis demonstrates that clinician-performed ultrasound remains the most cost-beneficial approach unless 100% of radiology-performed procedures can be performed on the day of referral. One-way sensitivity analysis also demonstrates that the complication rate of clinician-performed ultrasound-guided centesis does not influence the results of cost comparisons.

As of 1 August 2012, four courses in Australia were accredited by ASUM for the Certificate in Clinician Performed Ultrasound – Pleural Unit, collectively providing 184 training places per year. For the public health system, attendance at these courses is cost-neutral as physicians may access existing funding for professional development. Between 1 January 2011 and 31 December 2011, 124 ultrasound examinations were performed for pleural effusion by members of the Department of Respiratory Medicine at the Royal Melbourne Hospital, of which 68 subsequently led to ultrasound-guided pleural aspiration. This is sufficient to train six clinicians per annum to ASUM requirements. In 2011, 78 ‘principal referral hospitals’ in Australia provided a full range of medical services with an average bed capacity of over 400 beds and 45 000 separations per annum. In addition, seven university hospitals were identified in New Zealand. Assuming similar chest ultrasound volumes to our centre, there is sufficient capacity across the region to supervise up to 510 clinicians to competency in this technique per annum.

Discussion

Direct ultrasound localisation is supported by ample evidence and clear guidelines. Yet, our study found a significant gap between evidence and practice. One third of physicians practising adult respiratory medicine in Australia and New Zealand have not adopted direct ultrasound localisation. This issue is not unique to our region. Just a year prior to our survey, 48% of pleural procedures in the United Kingdom were performed without ultrasound guidance.

Clinicians often attribute evidence-into-action gaps to a lack of knowledge and respond with an ever-increasing cycle of disseminating evidence and guidelines. These efforts may be insufficient, for translational gaps often stem from blocks at multiple levels, including knowledge (individuals), expertise (teams), equipment (organisations) and available time (health systems). In our study, we therefore specifically examined each of these issues.

Our results indicate that a poor knowledge base only partially contributes to the problem. Most survey respondents were aware when they fell short of best practice; given no constraints, the majority of respondents (85.1%) would reduce iatrogenic risk by using direct ultrasound localisation. Most of these (78.0% overall) prefer clinician-performed ultrasound localisation, avoiding the inherent delays in radiology referral uncovered by our survey.

Lack of access is the main logistic barrier to direct ultrasound localisation. Direct ultrasound localisation can be undertaken either by either a radiologist or a trained clinician. Over 40% of respondents reported a delay of at least 2 days to obtain the procedure in radiology. Unfortunately, many physicians have no viable alternative as 48.6% also have no access to clinician-performed bedside ultrasound. Clinicians face the invidious choice between waiting for radiology (increasing length of stay) or proceeding with clinical localisation (risking complications).

Radiological delays aside, we demonstrated that constraints to clinician-performed bedside ultrasound centred on two issues. The first major impediment to bedside chest ultrasound relates to the unavailability of ultrasound equipment and its cost. The second relates to expertise. Half of all physicians who responded had received some form of ultrasound training, but only 4% reported sufficient expertise for independent chest ultrasound practice.

Both problems are eminently soluble. First, we have demonstrated that direct ultrasound localisation for pleural aspiration at the bedside is cost-beneficial by reducing both complications and bed days in hospital. Based on a purchase price of AUD $20 000 (includes...
machine, cart, probe and 5-year warranty; L Taylor, pers. comm., 2011), ultrasound equipment becomes cost-beneficial within approximately 25 procedures, well within the volume performed in the first 6 months at our centre. Cost-benefit will be reached even more quickly at centres with longer radiology delays; however, these cost-savings only apply where radiologist-performed cannot be performed on the same day as it is requested.

Our cost analysis can easily be adapted to local circumstances elsewhere. We provide them for our readers to champion bedside chest ultrasound when justifying capital expenditure within their institution.21

We have probably underestimated the true cost benefit because direct and indirect costs for radiology-performed procedures are almost certainly higher than ward-based procedures. We have also not accounted for the use of clinician-performed ultrasound to confirm or refute the presence of an effusion in whom clinical and chest radiograph assessment may have erroneously made this diagnosis, thus further reducing unnecessary procedures and delays.22,23 The potential for clinician-performed ultrasound to allow the reallocation of radiology resources has also not been considered.

Across the region, we identified 85 major referral centres that we assume have similar workloads to our own institution. Assuming 60 procedures per year at each site (based on our own annual volume of 68 aspirations), widespread introduction of clinician-performed ultrasound could potentially deliver health expenditure savings of over AU$15 million over a 5-year period because of reduced complications and shortened bed stays.

Regarding training, our estimates suggest that it would be possible to train the entire cohort of Australasian respiratory physicians (and advanced trainees) in less than 2 years, just by using existing courses and current procedure volumes. The one outstanding issue that must be addressed is ensuring sufficient access to radiology mentorship during training. Physician bodies such as the TSANZ should facilitate this by establishing formal links with radiologist and radiographer societies. There seems to be a clear case for the integration of chest ultrasound into the core training for advanced trainees in respiratory medicine.

Lack of time appears to limit the ability of private practitioners from performing bedside ultrasound. This may require a review of remuneration to provide incentives towards ultrasound-guided procedures (and disincentives for unguided procedures). Also, a small minority of physicians still prefer clinical localisation by choice. Promulgation of evidence and formal endorsement of international guidelines by the TSANZ will probably dissuade these practitioners from continuing this practice.

Our response rate of 53% lends credibility to our survey findings. However, clinicians with an interest in ultrasound are more likely to respond to a survey of ultrasound use. Furthermore, we only surveyed respiratory physicians who are current members of the TSANZ, but other subspecialty and general physicians who also perform pleural aspiration face similar barriers to best practice. It is therefore likely that our study underreports the real discrepancy between evidence and practice. Consequently, the scale of potential cost-savings may be even greater than estimated.

Conclusion

Direct ultrasound localisation for pleural aspiration is underutilised by respiratory physicians in Australia and New Zealand. Access to radiologist-performed ultrasound often involves substantial delay, and the availability of ultrasound equipment to enable clinicians to perform this technique regularly is limited.

We show that acquiring ultrasound equipment is cost-beneficial, and facilities are already in place to provide training and procedural experience to physicians in clinician-performed ultrasound. We urge respiratory physicians to initiate responsibly such services for the benefit of their patients.

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References


Supporting Information

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

Figure S1 Decision tree analysis comparing clinician-performed direct ultrasound localisation, radiologist-performed direct ultrasound localisation and clinical localisation for pleural aspiration.
Twenty-year trends in benzodiazepine dispensing in the Australian population

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Key words benzodiazepine, anxiolytic drug, hypnotic, sedative, defined daily dose, Ashton equivalent dose.

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Abstract

Aim: Considerable concern has been expressed about overprescribing of benzodiazepines and related harms. Past analyses have relied on World Health Organization-defined daily doses (DDD) which are sometimes out of keeping with clinical usage. This study examines 20-year (1992–2011) trends of benzodiazepine dispensing in Australia using both DDD and Ashton equivalent dose.

Methods: Data from the Drug Utilisation Sub-Committee and the Pharmaceutical Benefits Scheme (PBS) website were analysed. Trends in number of prescriptions, DDD/1000 people/day and DDD/prescription were examined over time, and between states/territories.

Results: In the 20-year period, 174 080 904 scripts were recorded, with temazepam the most dispensed benzodiazepine (35% of scripts), followed by diazepam (23%). Overall recorded utilisation fell from 27.7 DDD/1000 people/day in 1992 to 20.8 in 2011 (24.9% decrease). There were striking changes in use of individual benzodiazepines over time, with reductions in oxazepam and flunitrazepam and dramatic increases in alprazolam. Since 1998, there has been a steady increase, albeit modest, in per script DDD. The DDD/1000 people/day for items dispensed through PBS/Repatriation-PBS was highest in Tasmania and lowest in Northern Territory.

Conclusion: Despite a modest overall decline in the amount of benzodiazepine dispensed, the level of use is still likely to reflect relative over-prescribing given the paucity of accepted indications for long-term use. Since 1998, there was a polynomial increase in quantity dispensed per script. The WHO-defined DDD for clonazepam seems inappropriate and could impede monitoring of its abuse. Other problems include lack of national data for medications not subsidised on PBS/Repatriation PBS. A broad policy approach is required, not one which targets only one particular benzodiazepine.

Introduction

Benzodiazepines have long been used for conditions including insomnia, anxiety disorders, psychiatric emergencies, acute alcohol withdrawal, anaesthesia, intensive care and epilepsy.1,2 Prescribing benzodiazepines is seen as less problematic when used short term, and is associated with fewer side-effects and better safety than longer term use.3 However, there are increasing concerns about benzodiazepine use, particularly misuse, and dependence, with potentially life-threatening withdrawal symptoms,4 diminishing effect, tolerance and difficulty in discontinuing treatment.5 In older age, benzodiazepines also have serious adverse effects, including increased risk of mobility and activities of daily living problems,6 falling7 and a negative effect on cognitive functioning.8 They can cause sedation and impair balance and coordination, cognitive function and driving ability.9

Despite these known side-effects and reported misuse in Australia, as in most Western nations, benzodiazepines continue to be widely used. Data in 1991 showed an estimated 9.2 million benzodiazepine prescriptions were recorded in Australian retail pharmacies in that year alone, a quantity sufficient to provide a daily dose for 3% of the Australian adult population.10 This trend continued with data in 2005 showing that benzodiazepines were the most widely prescribed psychotropic medication in

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Australia, with diazepam, temazepam and oxazepam together making up nearly 4% of all prescriptions generated by general practitioners. Recent epidemiological studies have found high rates of antipsychotic, antidepressant and anxiolytic and sedative–hypnotic drug use among Australians. Previous studies of benzodiazepine use in Australia examined trends for relatively small intervals, but dispensing differences between states and trends in private prescription (for benzodiazepines not subsidised by the Pharmaceutical Benefits Scheme (PBS)) have rarely been reported, so only part of the picture has been available. Furthermore, the defined daily dose (DDD) index introduced by World Health Organization (WHO) to compare drug use may be misleading for some benzodiazepines. For instance, a DDD of 8 mg is listed for clonazepam, where the usual clinical dose is 0.5 mg, the DDD for oxazepam is listed as 50 mg where a more usual therapeutic dose is 30 mg. The strangely high DDD for a small number of benzodiazepines may mask high levels of utilisation. No previous study has examined benzodiazepine dispensing in Australia using another index of benzodiazepine dose.

The aim of this study was to examine 20-year (1992–2011) trends in benzodiazepine dispensing in Australia by using WHO DDD and the Ashton equivalent scale, and to describe the differences between states in dispensing of benzodiazepine derivatives, under both the PBS and Repatriation PBS (RPBS) schemes.

Methods

Data were collected from the dispensing database maintained by the Drug Utilisation Sub-Committee (DUSC). The DUSC database combines data on prescriptions subsidised under PBS/RPBS with estimates of non-subsidised prescriptions from Pharmacy Guild survey – an ongoing survey of 370 community pharmacies in Australia. Hence, compared with the database provided online by the PBS, the DUSC dispensing database offers more comprehensive information, capturing prescriptions for which the average dispensed price is below the patient co-payment threshold; drugs that are not subsidised by the PBS (including zolpidem, lorazepam, triazolam and clobazam); and prescriptions dispensed privately. Dispensing for individual states was collected through the PBS website, and so information was available for benzodiazepines dispensed under the PBS/RPBS only.

The quantity of each drug dispensed was standardised using the DDD/1000 people/day and population data from the Australian Bureau of Statistics. The DDD was established by the WHO Collaborating Centre for Drug Statistics Methodology and corresponds to an estimated mean daily dose of the drug when used for its main indication in adults. It allows for simple comparisons of drug use across countries and across different formulations of the drug. The DDD/1000 people/day is defined by the equation, where, , where is the number of prescriptions dispensed for a specific drug in a year, is the mass of each dose (e.g. milligrams or grams, expressed in the same unit as DDD), is the average dispensed quantity per prescription, is the mid-year Australian population for the year of data collection, is the number of days in the year.

The table developed by Ashton was used to calculate independently the equivalent dose of diazepam/1000 people/day. Microsoft Office Excel 2010 and STATA (release 11; StataCorp LP, College Station, TX, USA) were used for analyses.

Results

A total of 174 080 904 prescriptions was recorded in the 20 years (1992–2011) of interest. Temazepam was the most popular drug and accounted for the highest number of scripts (34.57%), followed by diazepam (22.90%). Temazepam, diazepam, oxazepam, nitrazepam and alprazolam constituted around 90% of all prescriptions and/or DDD dispensed in those 20 years. In terms of DDD/1000 people/day, diazepam was the most dispensed drug, followed by temazepam. Oxazepam, nitrazepam and alprazolam followed, respectively, as the other commonly dispensed drugs both in terms of prescriptions and DDD/1000 people/day (Table 1). However, following the Ashton equivalent dose, oxazepam (24.79%) was the most dispensed benzodiazepine, followed by diazepam (18.90%) and temazepam (16.30%). Clonazepam, which ranked seventh in terms of number of scripts, and tenth in terms of DDD/1000 people/day, was ranked fifth using the Ashton equivalent dose.
Seventy-one per cent of total DDD was dispensed through PBS/RPBS, 18% through private prescriptions and the remainder (11%) under a co-payment arrangement. Considering 20 years data, overall there has been a declining trend \( (P < 0.001) \) in benzodiazepine dispensing in Australia, and is largely consistent between WHO ATC/DDD and the Ashton equivalent diazepam dose scale (Fig. 1a). However, piecewise regression shows for the period 2002–2011 the declining trend is significant in WHO ATC/DDD equivalent dose \( (P < 0.01) \) but not in Ashton equivalent dose \( (P = 0.49) \). Prescription through PBS/RPBS has been declining continuously since 1999. A contrasting trend was observed for private prescription which, since 1999, began to rise and continued increasing apart from a small dip in 2007 (Fig. 1b). During the second half of the monitoring period (2002–2011), private prescription increased both in terms of number of prescriptions and DDD. During that period per year, private prescriptions were 1.6 times higher than in the previous period (1992–2001). In fact, since 2000, an inverse relationship between DDD of PBS/RPBS and privately dispensed items is evident, although the slope for the former is steeper than for the latter.

Diazepam was the most popular drug dispensed in almost all the years, comprising 22.90% of all benzodiazepine-related prescriptions written and 26.82% of DDD/1000 people/day dispensed (Table 1). Since the PBS listing of alprazolam in 1993, there has been a steady increase with a slight plateau from 2009. Temazepam started decreasing from 2000, a couple of years before the removal from PBS of temazepam 10 mg gelcaps. Zolpidem prescriptions rose steeply following its release in 2001, before decreasing markedly after 2007, the year Therapeutic Goods Administration (TGA) warned about bizarre sleep-related behaviours among those taking zolpidem.\(^{17} \) Year-wise dispensing trends of individual benzodiazepine derivatives are shown in Figure 2.

Year-wise DDD decreased until 2003 for both short and long half-life benzodiazepines and remained relatively stable afterward. The most dispensed formulations of diazepam, temazepam and alprazolam were the 5 mg, 10 mg and 1 mg tablet respectively.

Examination of only private prescriptions reveal that after its release in 2001, zolpidem gained a rapid rise in popularity increasing sharply from 155 924 in 2001 to 745 602 in 2006, and a sudden decline to less than 450 000 prescriptions in 2008, remaining almost static thereafter. Private prescriptions of temazepam, alprazolam and zopiclone were increasing, while flunitrazepam was already decreasing prior to reclassification from S4 to S8 in 2002. No noticeable change was evident for other preparations of benzodiazepines.

Twenty years of combined data show temazepam was the most dispensed benzodiazepine under PBS/RPBS with 47 983 079 prescriptions followed by diazepam (31 725 944) and oxazepam (28 113 774). However, of the private prescriptions, zolpidem (5 301 868) was the

### Table 1  Total prescriptions and defined daily dose (DDD)/1000 people/day for benzodiazepine preparations in Australia between 1992 and 2011

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Prescriptions recorded</th>
<th>WHO ATC/DDD</th>
<th>DDD/1000 people/day</th>
<th>Dose that is equivalent to 10 mg diazepam (Ashton table)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>%</td>
<td>Rank</td>
<td>Total</td>
</tr>
<tr>
<td>Temazepam</td>
<td>60 174 260</td>
<td>34.57</td>
<td>1</td>
<td>109.85</td>
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<tr>
<td>Diazepam</td>
<td>39 863 574</td>
<td>22.90</td>
<td>2</td>
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</tr>
<tr>
<td>Oxazepam</td>
<td>32 993 115</td>
<td>18.95</td>
<td>3</td>
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<tr>
<td>Nitrazapect</td>
<td>16 546 221</td>
<td>9.50</td>
<td>4</td>
<td>61.97</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>8 648 373</td>
<td>4.97</td>
<td>5</td>
<td>52.78</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>5 301 868</td>
<td>3.05</td>
<td>6</td>
<td>12.81</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>2 667 637</td>
<td>1.53</td>
<td>7</td>
<td>4.46</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>2 611 412</td>
<td>1.50</td>
<td>8</td>
<td>18.06</td>
</tr>
<tr>
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<td>1.15</td>
<td>9</td>
<td>5.05</td>
</tr>
<tr>
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<td>10</td>
<td>3.91</td>
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<tr>
<td>Bromazepam</td>
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<td>0.59</td>
<td>11</td>
<td>4.52</td>
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<tr>
<td>Clobazam</td>
<td>455 684</td>
<td>0.26</td>
<td>12</td>
<td>1.60</td>
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<tr>
<td>Midazolam</td>
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<td>0.11</td>
<td>13</td>
<td>0.09</td>
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<tr>
<td>Triazolam</td>
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<td>0.08</td>
<td>14</td>
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<tr>
<td>Clorazepate</td>
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<tr>
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<td>0.33</td>
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<tr>
<td>Flurazepam</td>
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<td>0.03</td>
<td>17</td>
<td>0.64</td>
</tr>
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<td>174 080 904</td>
<td>100.00</td>
<td></td>
<td>474.86</td>
</tr>
</tbody>
</table>

ATC, Anatomical Therapeutic Chemical Classification.
most dispensed preparation followed by temazepam (4,105,551) and flunitrazepam (2,335,082). Temazepam (8,085,630), diazepam (6,706,189) and oxazepam (2,642,422) remained the top three preparations dispensed under a co-payment arrangement.

Since 1998, overall there has been a steady increase, albeit slow, in per script DDD dispensed for all benzodiazepine types combined (Fig. 3). Per script DDD for PBS/RPBS and under co-payment dispensing has been increasing almost steadily since 1992. However, per script DDD for privately dispensed benzodiazepines sharply decreased until 2005 and then continued to increase. Piecewise regression indicated until 1998 significantly more prescriptions were written for benzodiazepine preparations for which the average dispensed DDD per script is relatively small ($P < 0.02$).

The number of benzodiazepine compounds available decreased from 15 in 1992 to 14 in 2011 and on the PBS/RPBS decreased from 11 in 1992 to 9 in 2011. Clorazepate, flurazepam and zopiclone and zolpidem were added in 1996 and 2001 respectively. Considering all benzodiazepine classes, the combined DDD/1000 people/day was 27.7 in 1992 and 20.8 in 2011, equating to a 24.9% decrease in dispensing over this interval. Comparison of major drugs dispensed in

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Figure 1  Year-wise total dispensing of benzodiazepine derivatives in Australia between 1992 and 2011 in terms of (a) defined daily dose (DDD)/1000 people/day (under co-payment (World Health Organization (WHO) DDD); private (WHO DDD); Pharmaceutical Benefits Scheme (PBS)/Repatriation PBS (WHO DDD); total (WHO DDD); total (Ashton manual) and (b) number of prescriptions.
1992 and in 2011 shows that diazepam not only sustained its position as the most popular benzodiazepine but also became more popular than it was 20 years prior. Temazepam, however, moved from the second to third most popular drug in 2011. Oxazepam decreased from 5.15 DDD/1000/day in 1992 to only 2.03 DDD/1000 people/day in 2011. Alprazolam became the second most popular drug in 2011 increasing substantially from 0.56 DDD/1000/day in 1992 to 4.52 DDD/1000 people/day in 2011, equating to more than an eightfold increase.

Statistics of statewide dispensing through PBS/RPBS show DDD/1000 people/day was highest in Tasmania and lowest in Northern Territory (Fig. 4). There was about fivefold difference in dispensing between states. However, a declining trend was documented in all the states since early 2000, with relatively sharp trends since 2009. The declining trends were highest in South Australia (1.8 and 1.1 DDD/1000 people/day), Tasmania (1.4 and 1.4 DDD/1000 people/day) and Victoria (1.0 and 1.3 DDD/1000 people/day), between 2009–2010 and

Figure 2 Dispensing trend of major benzodiazepine derivatives in Australia between 1992 and 2011 in terms of (a) defined daily dose (DDD)/1000 people/day and (b) 10 mg diazepam equivalent dose/1000 people/day.
2010–2011 respectively. These trends were very similar when quantity dispensed was measured using the Ashton equivalent dose.

**Discussion**

This study’s findings show that overall dispensing of benzodiazepines preparations has been decreasing over the last 20 years both in terms of total number of prescriptions and DDD/1000 people/day. Almost all major forms of benzodiazepines except alprazolam and diazepam displayed a decreasing trend. These findings are consistent with those of other smaller Australian analyses of data for 2002–2007 and for 2000–2011. The DDD index introduced by the WHO could be misleading for some derivates (e.g. clonazepam) and may underestimate the level of utilisation.

The decreasing trend in benzodiazepine dispensing is likely to be the result of a number of factors. First, although older people are the largest users of benzodiazepines and Australia has an ageing population, there has been considerable discussion about the risk of dependence and withdrawal symptoms for benzodiazepines, and growing practitioner and consumer awareness. Second, the increasing popularity of selective serotonin reuptake inhibitors (SSRI) and serotonin

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**Figure 3** Trend of per script defined daily dose (DDD) of benzodiazepine dispensing. (---), Overall DDD per script; (—), DDD per Pharmaceutical Benefits Scheme (PBS)/Repatriation PBS script; (—), DDD per private script; (—), DDD per underpayment script.

**Figure 4** Trends in dispensing of major benzodiazepines by state [in defined daily doses (DDD)/1000 people/day]. (---), NSW; (—), VIC; (—), QLD; (—), SA; (—), WA; (—), TAS; (---), ACT; (—), NT.
noradrenaline reuptake inhibitor (SNRI) for treatment of anxiety and depression may play a role.\textsuperscript{19,20} The use of SSRI was doubled between 2000 and 2011 and was the dominant category of antidepressant dispensed. Utilisation of SNRI, the second most prevalent category of antidepressant dispensed in 2011, and noradrenergic and specific serotonergic antidepressants also increased markedly. However, despite an overall declining trend, benzodiazepines have remained a major anxiolytic pharmacotherapy. Recent years have witnessed a dramatic increase in the use of other sedating pharmaceutical drugs such as quetiapine and risperidone including off label use for night sedation. The future trend to some extent will be determined by the availability and quality of alternative medications and of benzodiazepines in terms of their efficacy and addiction profile.

Temazepam dispensing for all the individual years still exceeded other preparations of benzodiazepines despite its declining trend. Subgroup analysis for temazepam showed a negative correlation between prescription frequency and average DDD (Qty \times Strength + DDD). Conversely, the reverse was true for diazepam, potentially explaining why diazepam, despite having less prescriptions than temazepam, had the highest DDD/1000 people/year. Clearly diazepam, the progenitor, remained popular both in terms of DDD/1000 people/year and absolute number of prescriptions over the 20-year period. Its popularity and market share mostly rests on 5 mg (PBS item 3162K) and 2 mg (PBS item 3161J) tablet preparations, and these two constituted more than 98% of diazepam prescriptions. Comparatively low strength and less reported side effects, early PBS listing and its use in treating alcohol and benzodiazepine dependence are possible reasons for the continuing widespread use of these preparations.

The increased dispensing of alprazolam may reflect the combined effects of its faster onset of action, clinician and patient preference, strong abuse potential\textsuperscript{21} and its recently increased use in the treatment of panic disorder.\textsuperscript{22} Although this drug did not receive any black-box warning (warning on the labelling of a prescription drug) from the TGA, the Medical Practitioners Board and the Royal Australian and New Zealand College of Psychiatrists now recommend that alprazolam has a very limited role in the treatment of panic disorder and anxiety, and that other means should be used as first line treatment.\textsuperscript{23} In particular, the increasing use of its 2 mg dose, which is equivalent to 20 mg diazepam, is raising questions as to whether it should be removed from PBS.\textsuperscript{24} This drug has recently been rescheduled to S8, a decision likely to reduce its utilisation, but that may lead to compensatory increased use of other benzodiazepines. Although the newer non-benzodiazepine Z-drugs, zolpidem and zopiclone are known to carry a lower risk of dependence,\textsuperscript{25} bizarre sleep-related disturbances (e.g. sleepwalking, sleep driving) in those taking zolpidem are documented.\textsuperscript{17} TGA warning, combined with the lack of PBS subsidy, may be responsible for the declining popularity of zolpidem.\textsuperscript{15} The long-term overview of benzodiazepines reveals that as the use of one formulation has decreased, another has taken its place. Declining use of flunitrazepam appears to have led to increased use of alprazolam. If alprazolam use declines as a result of action against that specific product, it seems likely that clonazepam or another agent will take its place which may not have lower toxicity. Since 2000, DDD of PBS/RPBS have decreased and privately dispensed items increased. Considering DDD as a proxy marker of pack size, this inverse relationship signals the possibility of an increasing use of private prescriptions to circumvent the controls imposed by the PBS standard pack sizes and/or the limitation of obtaining authority prescriptions. This suggests that to reduce use and abuse, regulatory action should apply across the whole class, and comprehensive changes in prescribing are required and should include public and prescriber education and live monitoring of prescribing and/or dispensing. Public and prescriber education is important as any regulatory action may eventually escalate the use and abuse of other similar medications as was witnessed in New York after triplicate regulation in 1989.\textsuperscript{26}

**Limitations**

Although the DUSC dispensing database is more comprehensive than the PBS database, it has some limitations. The DUSC database does not capture inpatient prescriptions in public hospitals. Also, data from 370-member pharmacies represent less than a 10th of pharmacies in Australia and may not necessarily reflect non-participating pharmacies. The diazepam equivalent dose given by Ashton applies to the acute use of benzodiazepines, and equivalence can vary with chronic use (where there is presence of active metabolites). However, given a major public health concern is acute toxicity, the scale is very relevant.

**Conclusion**

The results of this analysis suggest overall the number of prescriptions and the quantity (in DDD/1000 people/day) of benzodiazepines dispensed over the period 1992–2011 in Australia have been decreasing gradually in relative terms. Despite a declining trend in the total amount dispensed, benzodiazepine prescriptions remain at high frequency and average DDD (Qty × Strength + DDD). Considering DDD as a proxy marker of pack size, this inverse relationship signals the possibility of an increasing use of private prescriptions to circumvent the controls imposed by the PBS standard pack sizes and/or the limitation of obtaining authority prescriptions. This suggests that to reduce use and abuse, regulatory action should apply across the whole class, and comprehensive changes in prescribing are required and should include public and prescriber education and live monitoring of prescribing and/or dispensing. Public and prescriber education is important as any regulatory action may eventually escalate the use and abuse of other similar medications as was witnessed in New York after triplicate regulation in 1989.\textsuperscript{26}
levels, and quantity per script dispensed has increased. This is of concern particularly in the context of falling clinical indications and an increasing utilisation of alternative psychoactive medications. Within this declination, dispensing of some preparations decreased, and others increased. Rescheduling of alprazolam is due to take effect in 2014, but appears unlikely to influence overall benzodiazepine utilisation. The WHO defined DDD in this area is problematic as DDD of some drugs may impede monitoring of abuse. Proper regulatory measures across the whole class of benzodiazepines rather than individual preparations, prescriber and patient education and real-time monitoring of prescribing and dispensing are recommended.

Acknowledgement

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Increased cardiovascular risk in patients with severe mental illness

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Key words severe mental illness, cardiovascular, metabolic, mortality.

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Abstract

Background: People with severe mental illness (SMI) have a reduced life expectancy. A major cause of mortality is cardiovascular disease.

Aims: The aims of this study were to document the prevalence of cardiovascular risk factors in people with SMI engaged in community psychiatric rehabilitation and compare prevalence rates to the general, and Aboriginal and Torres Strait Islander (ATSI) populations of Australia.

Method: A cross-sectional audit was conducted on patients receiving care from Melbourne’s Inner-West Area Mental Health Service. Profiles were collected on: smoking status, body mass index, waist circumference, blood pressure, diabetic status and fasting lipid profiles. These were compared with the general and ATSI Australian populations.

Results: Complete data were available for 60 patients. Most were involuntary patients with a diagnosis of schizophrenia or schizoaffective disorder. Patients were more likely to smoke, be obese, have dyslipidaemia and the metabolic syndrome compared with the general and ATSI populations of Australia. Patients were more likely to have diabetes than the general population but had similar rates to the ATSI population. Patients had similar rates of hypertension to the general population but were less likely to be hypertensive compared with the ATSI population.

Conclusion: Australians living with SMI have very high rates of cardiovascular risk factors, far in excess of the general Australian population and comparable with the ATSI population.

Introduction

The mortality rate of people with severe mental illness (SMI) is two to three times that of the general Western population.1 This corresponds to a reduction in life expectancy by 10–25 years, a figure that is comparable with that of the Aboriginal and Torres Strait Islander (ATSI) population of Australia. This mortality gap appears to have widened in recent decades.2 A major contributor to this excess mortality is cardiovascular disease (CVD), and people with SMI are almost two times more likely to die from CVD.3,4

An increased prevalence of modifiable cardiovascular risk factors has been reported in SMI populations. People with SMI are more likely to smoke, be overweight or obese, have high blood pressure, insulin resistance or diabetes, high cholesterol, and have the metabolic syndrome (MetS).5–7 Reasons for this are numerous and wide-ranging. They include: (i) symptoms of mental illness (e.g. negative symptoms of schizophrenia, such as low motivation levels); (ii) other co-occurring mental health diagnoses (e.g. depression, anxiety and substance-use disorders); (iii) comorbid physical illness (e.g. musculoskeletal complaints); (iv) suboptimal lifestyle factors, including a poor diet, sedentary behaviour and a reduced ability to quit smoking; (v) low socioeconomic status and unemployment, which are known to be associated with increased cardiovascular risk; (vi) deficits in the monitoring and proactive treatment of CVD risk factors by health workers; and (vii) the adverse metabolic effects of antipsychotic and mood-stabilising agents used to treat SMI.8–11

In people who have schizophrenia, international prevalence rates for modifiable CVD risk factors and their relative risks (RR) compared with the general Western population are: smoking 50–80% (RR 2–3), obesity 45–55% (RR 1.5–2), hypertension 19–58% (RR 2–3), diabetes 10–15% (RR 2), dyslipidaemia 25–69% (RR ≤5) and MetS 37–63% (RR 2–3).12 Galletly et al. have recently published a prevalence study examining CVD risk factors in an Australian cohort of patients with psychotic disorders. Assessing over 1000 patients nation-wide, they...
found that 67% smoked, 76% were overweight or obese, 47% had hypertension, 40% had abnormal glucose metabolism including diabetes, one third had raised cholesterol, and 55% had MetS.13

To the best of our knowledge, our study is the first to examine the prevalence of cardiovascular risk factors in patients with SMI who are currently engaged exclusively in psychiatric intensive community rehabilitation. We also compare the prevalence of these cardiovascular risk factors to the general Australian population (GAP) and the ATSI population of Australia for the first time.

Methods

A cross-sectional audit of the medical files was conducted on all patients who were receiving care from Melbourne’s Inner West Mobile Support and Treatment Team, and Community Care Unit (CCU) in May 2012. Both public mental health services provide psychiatric treatment, case management and intensive community rehabilitation to patients with SMI. The CCU also provides residential care.

The smoking status, height, weight, waist circumference, blood pressure, fasting blood glucose level, 2-h oral glucose tolerance test (where relevant) and fasting lipid profiles were obtained from the medical files of each patient. These data are routinely collected and documented as part of the service’s standard ‘metabolic monitoring’ protocol. Basic demographic data for each patient were also collected from the medical file. Ethics approval was not required for this audit.

Current smokers were grouped as either ‘yes’ or ‘no’, where ‘yes’ equated to daily cigarette smoking. Body mass index was calculated using height (cm) and weight (kg) measurements and grouped into underweight (<18.5), normal weight (18.5–24.9), overweight (25–29.9) or obese (≥30). Hypertension was defined as a systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg, or on antihypertensive medication for a previous diagnosis of hypertension. Patients who had a fasting glucose of ≥5.6 mmol/L went on to have an oral glucose tolerance test. Diabetes was defined as a fasting glucose of ≥7.0 or a 2-h glucose tolerance ≥11.1, or a previous diagnosis of diabetes. Impaired glucose tolerance (IGT) was defined as a 2-h glucose tolerance of ≥7.8 but <11.1. Impaired fasting glucose (IFG) was defined as a fasting glucose of ≥5.6 but <7.0 and a normal 2-h glucose tolerance test. Normal glucose metabolism was defined as a fasting glucose of <5.6. The MetS was defined using the International Diabetes Federation criteria. These criteria require an abnormal waist circumference (≥94 cm in men, ≥80 cm in women) plus two or more of (i) elevated blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic, or on treatment of a previous diagnosis of hypertension), (ii) low HDL (<1.03 mmol/L in men, <1.30 mmol/L in women) on treatment for this abnormality), (iii) high triglycerides (≥1.7 mmol/L or on treatment of this abnormality) and (iv) IFG (≥5.6 mmol/L or a previous diagnosis of diabetes).

GAP and ATSI population data were collected from various sources.14–22 Where prevalence data were published in percentages only, raw numbers were estimated from the quoted study sample sizes for the purposes of calculating RR. Statistical analysis was conducted using the software program Prism 5.0 (GraphPad, La Jolla, CA, USA). RR figures were calculated using the Chi-squared test with a paired two-tailed t-test to calculate 95% confidence intervals and P values.

Results

Patient population

Complete or near-complete data were available for 60 out of a total of 66 current patients at the time of the audit. Waist circumference measurements were available for 56 patients. Where data were unavailable, patients either refused or were unavailable for an examination and/or fasting blood test. Demographic data are detailed in Table 1. Most patients had a diagnosis of either schizophrenia (63%) or schizoaffective disorder (33%), and most were treated under the Victorian Mental Health Act as involuntary patients. Half the cohort was treated with clozapine as their primary antipsychotic, and 65% of patients were on two or more significant psychotropic agents.

Prevalence of cardiovascular risk factors in this patient population (Table 1)

Two-thirds of SMI patients smoked, half the cohort was obese, and another third was overweight. One fifth of patients were found to be hypertensive, and a further 20% had borderline hypertension (systolic BP 130–139 mmHg or diastolic BP 85–89 mmHg). Ten patients had diabetes, a further four patients had IGT and eight had IFG. The prevalence of MetS was 66%. Increased waist circumference, combined with low HDL and high triglycerides, was the most common pattern noted (Table 2). Only 10 patients had a normal lipid profile, when the National Heart Foundation guidelines were applied (triglycerides <1.5, LDL <2.5, HDL >1.0).23 Fifteen patients were on lipid-lowering therapy, but 11 of these patients had persistent dyslipidaemia despite their treatment. Most patients (35) had untreated dyslipidaemia. Of these, treatment would be recommended for 29, as per Therapeutic Guidelines’ Cardiovascular Expert Group.24 Eight of these untreated patients were eligible for Pharmaceutical...
Table 1 Characteristics of the studied patient population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n = 60)</th>
</tr>
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<td>Basic demographics</td>
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<td>Age, mean (SD; range) (years)</td>
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<tr>
<td>Male, n (%)</td>
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</tr>
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<td>Aboriginal and Torres Strait Islander</td>
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<td>Public housing</td>
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<td>Community care unit</td>
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<td>Supported residential service</td>
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<td>Employment status, n (%)</td>
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<td>Disability support pension (DSP)</td>
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<td>Schizophrenia</td>
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<td>Schizoaffective disorder</td>
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<td>Other</td>
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<td>Involuntary, n (%)</td>
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<td>Clozapine</td>
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<td>Olanzapine</td>
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<td>Other</td>
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<td>+1 additional antipsychotic</td>
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<td>+1 mood stabiliser</td>
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<tr>
<td>+2 or more additional agents (antipsychotic or mood stabiliser)</td>
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<tr>
<td>Cardiovascular risk factor profile, n (%)</td>
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<td>Smoking</td>
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<tr>
<td>Impaired glucose metabolism</td>
<td>22 (36)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>20 (33)</td>
</tr>
<tr>
<td>Metabolic syndrome (n = 56)</td>
<td>37 (61)</td>
</tr>
</tbody>
</table>

SD, standard deviation.

Benefits Scheme (PBS) subsidisation for lipid-lowering therapy but were not receiving lipid-lowering medication.

Comparisons to the general Australian and ATSI populations (Table 3)

Patients with SMI were more likely to smoke, be obese and have MetS compared with both the GAP and the ATSI population. Patients were equally as likely to be hypertensive compared with the GAP and less likely to be hyper-

Discussion

This study examined the prevalence of cardiovascular risk factors in patients with SMI engaged in intensive community outreach psychiatric rehabilitation. This cohort of patients demonstrated a particularly disadvantaged subpopulation – most were living on government welfare payments in public housing or supported accommodation. Most were involuntary patients under the Victorian Mental Health Act, and all were treated with one or more antipsychotics, with or without a mood stabiliser. Half was treated with clozapine, which is reserved for treatment-resistant psychotic illness only and is well known for its propensity for weight gain and metabolic side-effects including dyslipidaemia and insulin resistance.21 Despite intensive psychiatric rehabilitation, which includes attention to basic lifestyle interventions including diet and exercise, we found alarmingly high prevalence rates of cardiovascular risk factors.

Our results are consistent with the large national survey by Galletly et al. (2012) of over 1000 persons with SMI.13 We report an identical smoking prevalence of 67%. Galletly et al. found that 46% were obese and 29% were overweight, whereas we report slightly higher figures: 50% were obese, and 33% were overweight. They quote a higher hypertension prevalence rate of 47.5%, where hypertension was defined as a systolic BP ≥130 or a diastolic BP ≥85 or on treatment for previously diagnosed hypertension. Using this definition, we found 40% of our sample was hypertensive. Galletly et al. did not provide information on the number of diabetics in the cohort but did report that 40% of patients had impaired glucose metabolism (fasting glucose ≥5.6 or diabetes). Using this criterion, we found that a similar
Gladigau et al.

Table 3 Cardiovascular risk factor prevalence: SMI compared with GAP and ATSI

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>General Australian population</th>
<th>ATSI</th>
</tr>
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<tbody>
<tr>
<td>%</td>
<td>SMI versus GAP</td>
<td>%</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>P-value</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Smoking</td>
<td>19</td>
<td>3.5 (2.9–4.2)</td>
</tr>
<tr>
<td>Obesity</td>
<td>25</td>
<td>2.0 (1.6–2.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>29</td>
<td>0.7 (0.4–1.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7</td>
<td>2.3 (1.3–4.0)</td>
</tr>
<tr>
<td>MetS</td>
<td>31</td>
<td>2.1 (1.8–2.6)</td>
</tr>
</tbody>
</table>

ATS1, Aboriginal and Torres Strait Islander; CI, confidence interval; GAP, general Australian population; MetS, metabolic syndrome; RR, relative risk; SMI, severe mental illness.

proportion (36%) of our sample had abnormal glucose metabolism. We report a higher prevalence of MetS (66%) compared with 55%, as found by Galletly et al. These observed similarities give additional weight to the comparisons we have made between the SMI, GAP and ATSI populations.

In comparison with the GAP, we found that this SMI cohort had a significantly increased prevalence of smoking, obesity, diabetes and the MetS, and most patients had untreated or undertreated dyslipidaemia. In comparison with the ATSI population of Australia, our patients were more likely to smoke, be obese and have the MetS and were equally as likely to have diabetes. Interestingly, our cohort tended to have lower rates of hypertension. This may be secondary to treatment with clozapine, which is known to cause orthostatic hypotension. Certainly, it is the first author’s anecdotal observation that those treated with clozapine tended to have lower blood pressures. This may form an area of future research.

There are some limitations to this study. First, reported prevalence rates were unadjusted for age and sex (comparison prevalence rates in GAP and ATSI were also unadjusted for age and sex), and we have examined a relatively young cohort of patients (mean age, 39 years; range, 20–56 years). However, given that the prevalence of obesity, hypertension, diabetes, dyslipidaemia and MetS all increase with increasing age, it is reasonable to assume that observed differences between SMI and GAP might be greater if the figures are adjusted for age and sex. Second, a variety of sources for ATSI prevalence data was used, as referenced in Methods, as no individual source was able to provide all the necessary information, and each source is subject to its own limitations. For example, body mass index data were obtained from the Australian Bureau of Statistics and relied on self-reporting. Hypertension data (measured) were sourced from a study of 436 ATSI persons in Central Australia. Diabetes data came from a study of urban ATSI persons in Darwin, and MetS data were sourced from indigenous communities in northern Queensland. Yet, despite the studied SMI population residing in Melbourne’s Inner West area, where patients should have very good access to primary healthcare in comparison with rural or remote ATSI persons, we report a largely similar prevalence of major cardiovascular risk factors.

Danish research has recently found that the life expectancy for people with schizophrenia is 57.8 years for men and 64.6 years for women.25 This is similar to the ATSI population of Australia, where the life expectancy is 59.6 years, corresponding to a gap of 23.2 years compared with the GAP.26 A primary cause for this increased mortality in both groups is CVD. To date, the response to the inequalities existing between the ATSI population and the GAP has been encouraging.

Several key initiatives have been implemented in several different areas in an effort to ‘close the gap’ between the adverse health statistics of the ATSI population compared with the GAP. For example, unique Medicare Benefits Schedule item numbers have been introduced to encourage the provision of optimal primary healthcare to ATSI people. Also, ATSI persons qualify sooner for lipid-lowering therapy under the PBS, and lowering lipids using prescribed medication (in particular, using a statin) is increasingly being recognised as a very effective way to reduce mortality from CVD.27 Given that patients with SMI are less able to incorporate optimal diet and exercise regimes into their everyday lives, combined with the fact that the very medication used to treat their mental illness adversely affects their lipid profiles, granting easier access to lipid-lowering therapy may be a particularly cost-effective intervention overall.

Conclusion

Our data reaffirm that patients with SMI have significant cardiovascular risk factors that are likely to contribute to their early death. Further, the extent and degree of these risk factors are comparable with that in the ATSI community. The ATSI population is appropriately recognised as a ‘Special Needs Group’. We believe the SMI population should be accorded a similar status.
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Cardiac sarcoidosis: the Christchurch experience
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Key words
sarcoidosis, cardiac, cardiac magnetic resonance imaging, arrhythmia, pacemaker.

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Abstract

Background and aims: To present an overview of the diagnosis, treatment and outcomes of patients with cardiac sarcoidosis managed in Christchurch Hospital, New Zealand.

Methods: A retrospective review of patients with cardiac sarcoidosis at Christchurch Hospital from January 2005 to December 2012.

Results: Eighteen patients were identified with cardiac sarcoidosis. All the 12 patients that underwent cardiac magnetic resonance imaging (CMR) had abnormal scans. Angiotensin-converting enzyme (ACE) levels were elevated in 4 of 16 patients and troponin (cTn) was elevated in 5 of 15 patients. Endomyocardial biopsies were diagnostic in two of six patients. The principal causes for presentation related to symptomatic high-grade atrioventricular conduction block and congestive heart failure with six patients in each of these groups. In addition, three patients presented with ventricular tachycardia and the remaining three patients presented with atrial fibrillation, recurrent presyncope without proven heart block and an asymptomatic persistent elevation of cardiac troponin. Seven patients had pre-existing, extra-cardiac sarcoidosis and a concomitant diagnosis was made in a further eight cases. Three patients had isolated cardiac involvement at presentation. Sixteen patients received immunosuppressive therapy. Twelve patients had cardiac devices implanted; five pacemakers, five defibrillators and two resynchronising pacemaker defibrillators. During follow up for 0.1–30.8 years, median 4.8 years, two patients died.

Conclusions: In our patients CMR demonstrated high diagnostic sensitivity, while biomarkers (ACE and cTn) were frequently within the normal reference range. Cardiac sarcoidosis caused major arrhythmias or heart failure in the majority of patients. Most patients were treated with immunosuppression and cardiac device therapy. Long-term mortality was lower than previously reported.

Introduction

Sarcoidosis is a multi-system disorder characterised by the formation of non-caseating granulomas. Recognition of cardiac involvement did not occur until 1929, a full 60 years after the cutaneous manifestations of the condition were recognised by Jonathan Hutchinson. This may be because symptomatic cardiac involvement is only recognised in 2% of patients with extra-cardiac sarcoidosis although post-mortem investigations identify myocardial disease in 20–25% of the total sarcoidosis cohort. Perhaps, reflecting the challenge of identifying cardiac involvement, early descriptions based on autopsy studies described a very poor prognosis with 65% of cases manifesting as sudden cardiac death. As non-invasive diagnostic strategies have emerged, more recent studies have tended to demonstrate an improved prognosis with 5-year survival rates in excess of 50%.

The diagnosis of cardiac sarcoidosis can be difficult though it has been improved by cardiac magnetic resonance (CMR) scanning. Guidelines for diagnosis were originally prepared by the Japanese Ministry of Health and Welfare in 1993 and revised by the Japanese Society of Sarcoidosis and other Granulomatous Disorders in 2006 (Table 1). Despite these guidelines, cardiac sarcoidosis remains an incompletely defined and likely under-recognised condition.

Cardiac sarcoidosis is rare in Australasia with no cases reported in a series of 122 cases of sarcoidosis reported in 2007 by Gillman and Steinfort. Twenty Australian patients with cardiac sarcoidosis have been reported by
Allen, but we are not aware of any recent published Australasian cohorts of cardiac sarcoidosis with long-term follow up.

This report presents our experience of cardiac sarcoidosis in a tertiary teaching hospital in Christchurch, New Zealand.

Methods

Study design

We undertook a retrospective, systematic chart review of patients with cardiac sarcoidosis who were under the care of the Cardiology Department of Christchurch Hospital between January 2005 and December 2012.

Patient selection

We identified patients by systematically searching the electronic echocardiographic records at Christchurch Hospital for reports including the terms ‘sarcoid’ or ‘sarcoidosis’ in the referral indication or study findings. The clinical records (both physical and electronic) of these patients were then reviewed to assess whether they had been diagnosed prior or subsequently with sarcoidosis. Patients without evidence of cardiac involvement were excluded. Patients were included if they had had sufficient evidence to satisfy their treating cardiologist that a diagnosis of cardiac sarcoidosis was appropriate. We did not require patients to fit any particular diagnostic criteria to be included in the audit. Typically, the diagnosis was made based on a constellation of clinical, biochemical, radiological and histological features.

Data acquisition

We retrospectively reviewed the outpatient and inpatient clinical records including those from referring hospitals to identify patient demographics, date and manner of presentation; investigations performed and diagnostic procedures undertaken; treatments, both pharmacological and with cardiac devices; subsequent clinical course and complications arising from the disease itself or our treatments. The diagnostic findings were assessed to determine if patients met the Japanese Society of Sarcoidosis and other Granulomatous Disorders sarcoidosis diagnostic guidelines (Table 1).

Results

Patients and diagnosis

Ninety-four patients who were referred for an echocardiogram at Christchurch Hospital between 2005 and 2012 had either of our search terms in the indication or findings section of their reports. The majority of these patients had sarcoidosis involving extra-cardiac organ systems. Eighteen patients were diagnosed by their clinician as having cardiac sarcoidosis and are the subject of this report. However, of these 18 patients, only 7 (39%) fulfilled the Japanese Society of Sarcoidosis and other Granulomatous Disorders sarcoidosis diagnostic guidelines (Table 1).

<table>
<thead>
<tr>
<th>Table 1 Revised guidelines for diagnosing cardiac sarcoidosis 2006 (Japan Society of Sarcoidosis and other granulomatous disorders)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Histological diagnosis group</td>
</tr>
<tr>
<td>Cardiac sarcoidosis is confirmed when myocardial biopsy specimens demonstrate non-caseating epithelioid cell granuloma with histological or clinical diagnosis of extra-cardiac sarcoidosis.</td>
</tr>
<tr>
<td>2. Clinical diagnosis group</td>
</tr>
<tr>
<td>Although myocardial biopsy specimens do not demonstrate non-caseating epithelioid cell granuloma, extra-cardiac sarcoidosis is diagnosed histologically or clinically and satisfies the following conditions and more than one in six basic diagnostic criteria.</td>
</tr>
<tr>
<td>(1) More than two of four major criteria are satisfied.</td>
</tr>
<tr>
<td>(2) One in four major criteria and more than two in five minor criteria are satisfied.</td>
</tr>
<tr>
<td>Major criteria</td>
</tr>
<tr>
<td>(a) Advanced AV block.</td>
</tr>
<tr>
<td>(b) Basal thinning of the interventricular septum.</td>
</tr>
<tr>
<td>(c) Positive cardiac 67Ga uptake.</td>
</tr>
<tr>
<td>(d) Depressed ejection fraction of the left ventricle (LVEF &lt;50%).</td>
</tr>
<tr>
<td>Minor criteria</td>
</tr>
<tr>
<td>(a) Abnormal ECG findings: ventricular arrhythmias (VT, multifocal or frequent PVC), RBBB, axis deviation or abnormal Q-wave.</td>
</tr>
<tr>
<td>(b) Abnormal echocardiography: regional abnormal wall motion or morphological abnormality (ventricular aneurysm, wall thickening).</td>
</tr>
<tr>
<td>(c) Nuclear medicine: perfusion defect detected by 201Tl myocardial scintigraphy or 99mTc myocardial scintigraphy.</td>
</tr>
<tr>
<td>(d) Gd-enhanced MRI: delayed enhancement of myocardium.</td>
</tr>
<tr>
<td>(f) Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration over moderate grade.</td>
</tr>
</tbody>
</table>

AV, atrioventricular; ECG, electrocardiograph; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PVC, premature ventricular complex; VT, ventricular tachycardia
One patient had evidence of isolated cardiac sarcoidosis only, and two patients who presented with isolated cardiac sarcoidosis developed evidence of multi-organ involvement at a later date. The principal causes of presentation related to congestive heart failure (six cases, 33%) and presyncope related to high-grade atrioventricular (AV) heart block (six cases, 33%). Three patients (17%) presented with sustained ventricular tachycardia (VT). The three remaining cases had atrial fibrillation, recurrent presyncope with suspicion of (but not confirmed) AV conduction defect and persistently elevated cardiac troponin in a patient with pre-existing respiratory sarcoidosis.

Because of the wide time frame over which our patients presented, there was diversity with regard to the initial investigations undertaken. All patients had a 12-lead electrocardiograph (ECG). This initial ECG was unremarkable in two cases only. In addition to the rhythm disturbances mentioned above, there was one patient with first degree AV block and two each with right bundle branch block and 2:1 AV block.

Angiotensin-converting enzyme (ACE) levels were measured in 16 patients. These were elevated above the reference range in four cases (25%). Cardiac-specific troponin enzymes were elevated above the reference range in five of 15 patients (33%).

All patients were assessed with a chest radiograph. This showed evidence of sarcoidosis affecting the pulmonary interstitium or thoracic lymph nodes in seven cases. Sixteen patients received a computed tomography scan of their chest which was normal in only two cases. Four patients had evidence of lymphadenopathy. The remaining 12 had changes involving the lung parenchyma in addition to lymphadenopathy.

The results of an echocardiogram at the time of first diagnosis were available for 17 patients. The median left ventricular ejection fraction (LVEF) was 58%. Six patients had impaired left ventricular systolic function (LVEF < 50%).

Twelve patients were investigated with CMR scans. All were abnormal with characteristic areas of delayed gadolinium enhancement (DGE) in 10 of the 11 cases that used this contrast agent. The remaining two scans (one without gadolinium contrast) demonstrated biventricular dilatation with severely impaired systolic function.

Histological sampling was performed in nine patients (53%). Transbronchial samples were obtained in four cases and demonstrated non-caseating granulomas in three. Endomyocardial biopsies (EMB) were obtained (exclusively from the right ventricle) in six patients. Two of these samples were diagnostic with non-caseating granulomas and multinucleate giant cells identified.

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### Table 2: Patient characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Principal cause of presentation</th>
<th>Multi-organ involvement</th>
<th>ECG</th>
<th>Positive ACE</th>
<th>Positive cTn</th>
<th>LVEF (%)</th>
<th>CMR findings</th>
<th>EMB result</th>
<th>JSOGD Criteria fulfilled</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/62</td>
<td>62</td>
<td>AF Pre-existing</td>
<td>AF</td>
<td>No</td>
<td>No</td>
<td>62</td>
<td>Focal DGE</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>F/29</td>
<td>29</td>
<td>CHF Pre-existing</td>
<td>RBBB</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>F/33</td>
<td>33</td>
<td>High-grade AV block Concomitant</td>
<td>High-grade AV block</td>
<td>No</td>
<td>No</td>
<td>77</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>F/58</td>
<td>58</td>
<td>High-grade AV block Concomitant</td>
<td>High-grade AV block</td>
<td>No</td>
<td>No</td>
<td>75</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>M/31</td>
<td>31</td>
<td>Presyncope Concomitant</td>
<td>1' AV block</td>
<td>No</td>
<td>N/A</td>
<td>58</td>
<td>Multifocal DGE</td>
<td>Positive</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>F/53</td>
<td>53</td>
<td>High-grade AV block Concomitant</td>
<td>High-grade AV block</td>
<td>N/A</td>
<td>N/A</td>
<td>79</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>M/61</td>
<td>61</td>
<td>CHF Concomitant</td>
<td>RBBB</td>
<td>No</td>
<td>No</td>
<td>19</td>
<td>Biventricular dilatation and impairment</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>M/48</td>
<td>48</td>
<td>SVT + NSVT Pre-existing</td>
<td>AVNRT + NSVT</td>
<td>No</td>
<td>No</td>
<td>71</td>
<td>Multifocal DGE</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>F/61</td>
<td>61</td>
<td>CHF Concomitant</td>
<td>NSR</td>
<td>No</td>
<td>No</td>
<td>20</td>
<td>N/A</td>
<td>Negative</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>M/31</td>
<td>31</td>
<td>AV block + NSVT Concomitant</td>
<td>High-grade AV block</td>
<td>No</td>
<td>Yes</td>
<td>58</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>M/42</td>
<td>42</td>
<td>VT Subsequent</td>
<td>VT</td>
<td>Yes</td>
<td>Yes</td>
<td>41</td>
<td>Multifocal DGE</td>
<td>Equivocal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>F/40</td>
<td>40</td>
<td>CHF Pre-existing</td>
<td>RBBB</td>
<td>No</td>
<td>Yes</td>
<td>17</td>
<td>Multifocal DGE</td>
<td>Equivocal</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>M/62</td>
<td>62</td>
<td>CHF Pre-existing</td>
<td>High-grade AV block</td>
<td>Yes</td>
<td>No</td>
<td>20</td>
<td>Multifocal DGE</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>M/44</td>
<td>44</td>
<td>VT Concomitant</td>
<td>VT</td>
<td>Yes</td>
<td>Yes</td>
<td>55</td>
<td>Multifocal DGE</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>M/55</td>
<td>55</td>
<td>Positive cTn Pre-existing</td>
<td>NSR</td>
<td>No</td>
<td>Yes</td>
<td>59</td>
<td>Multifocal DGE</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>M/52</td>
<td>52</td>
<td>High-grade AV block Concomitant</td>
<td>2:1 AV block</td>
<td>No</td>
<td>No</td>
<td>73</td>
<td>Multifocal DGE</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>M/44</td>
<td>44</td>
<td>High-grade AV block Isolated CS</td>
<td>2:1 AV block</td>
<td>No</td>
<td>No</td>
<td>71</td>
<td>Multifocal DGE</td>
<td>Positive</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AV, atrioventricular; AVNRT, atrioventricular nodal re-entrant tachycardia; CHF, congestive heart failure; CMR, cardiac magnetic resonance imaging; cTn, cardiac troponin; DGE, delayed gadolinium enhancement; EMB, endomyocardial biopsy; JSOGD, Japanese Society of Sarcoidosis and Other Granulomatous Disorders; LVEF, left ventricular ejection fraction; N/A, not available; NSR, normal sinus rhythm; NSVT, non-sustained VT; RBBB, right bundle branch block; SVT, supraventricular tachycardia; VT, ventricular tachycardia.
Three patients had non-specific EMB results showing patchy interstitial fibrosis. One patient had normal myocardium only on tissue samples.

**Treatment and clinical course**

Sixteen patients were initiated on oral glucocorticoid therapy following their diagnosis. Typically, this consisted of high-dose (40–60 mg per day) prednisone. The duration of treatment was prolonged with slowly tapered doses over a period of 6 to 24 months.

Three patients received azathioprine in addition to prednisone as a steroid-sparing agent.

With regards to complications arising from these immune modifying agents, we identified five patients with reduced bone mineral density, one with significant glucocorticoid-related weight gain and one case of steroid-induced diabetes mellitus.

In addition to pharmacological treatments, 12 patients had cardiac devices implanted. Five patients received permanent pacemakers, five received implantable cardiac defibrillators and two received cardiac resynchronisation pacemakers-defibrillators.

In the four cases where initial ACE levels were elevated, the levels normalised after starting immunosuppressants. Similarly, in patients with elevated troponins, serial cardiac troponin levels fell over time although often took longer to normalise (median 104 days) after starting immunosuppressants. We also found several patients with an association between discontinuation of therapy and new elevation of troponin levels.

Repeat echocardiography demonstrated a greater than 10% increase in LVEF in four of the six patients with impaired systolic function at baseline.

Two patients had repeat CMR imaging. In one case, this showed a significant reduction in the volume of myocardium-exhibiting DGE over a period of 4 months of immunosuppressive therapy. The other patient developed a new area of DGE where none had been present 13 months earlier despite intervening steroid therapy.

Two patients (11%) died during the follow-up period of 4.8 years (median). One died from progressive respiratory failure related to pulmonary sarcoidosis 31 years after their presentation with cardiac symptoms. The second case related directly to cardiac involvement causing a progressive dilated cardiomyopathy with death occurring 14 years after presentation.

**Discussion**

We present our experience with cardiac sarcoidosis. Our observational series demonstrates some of the challenges in the diagnosis and management of cardiac sarcoidosis.

Cardiac sarcoidosis is a condition that has traditionally been poorly defined and likely under recognised. The clinical manifestations relate to the localisation and extent of distribution of granulomas throughout the heart. Disease affecting the conduction system presents with varying degrees of atrioventricular conduction block, whereas involvement restricted to the myocardium may give rise to ventricular arrhythmias or congestive heart failure. Diagnostic criteria have been proposed by the Japanese Society of Sarcoidosis and other granulomatus disorders (Table 1) and require either a positive cardiac biopsy or clear extra-cardiac sarcoidosis with multiple cardiac clinical/imaging criteria. The majority of our patients failed to fulfil these criteria, suggesting the criteria may have poor sensitivity. Subclinical involvement also exists and may be detected in asymptomatic patients with a variety of biochemical, radiological or electrocardiographic investigations.

Our cases presented as a heterogeneous group with symptoms attributable to both brady- and tachyarrhythmias as well as primary myocardial dysfunction. These presentations are common relative to the incidence of cardiac sarcoidosis and sarcoidosis could therefore easily be overlooked as a possible aetiology during the diagnostic assessment. The relative youth of our patients reinforces the general guidance to consider the diagnosis in patients presenting with these problems at a young age.

The high rate of concomitant diagnosis of pulmonary or lymph node involvement supports the routine use of CT imaging of the chest as part of the initial assessment. Certainly, finding evidence of other organ involvement greatly assists in diagnosing sarcoidosis with cardiac involvement. However, as a recent observational series reviewing histologically proven cardiac sarcoidosis reported single organ involvement in 63% multi-organ involvement is not necessary for a diagnosis.

The variable natural history of sarcoidosis makes it difficult to correlate apparent clinical improvement as a result of specific therapies. We attempted to monitor treatment response with a variety of indices. Granulomata, including those due to sarcoidosis, produce ACE that can be measured in serum. While previous reports have stressed the diagnostic utility of serum ACE levels in sarcoidosis, we found serum ACE levels to be of limited diagnostic sensitivity as has also been noted in a contemporary review. It may be that previous treatment of extra-cardiac sarcoidosis had suppressed these levels prior to their subsequent cardiac presentation, or the burden of granulomata was not great enough to elevate serum levels. However, we did observe that in the minority of patients with elevated ACE levels, they fell promptly with immunosuppression suggesting a
beneficial effect of immunosuppression on disease activity and a monitoring role for serum ACE levels.

The utility of CMR imaging, principally using gadolinium (Gd) contrast, was particularly noteworthy. T2-weighted images and early Gd-enhanced images demonstrate high-signal intensity in areas of myocardial oedema or inflammation. Late Gd enhancement occurs in regions of inflammation and fibrous myocardial replacement. The typical distribution of these changes in the mid-myocardium is in contrast with the subendocardial pattern seen in ischaemic cardiomyopathies. All of our patients demonstrated significant abnormalities with this investigation. This is in keeping with several other studies demonstrating an apparent sensitivity of 75–100%. By differentiating active inflammation from irreversibly scarred myocardium, CMR may have prognostic value, and the apparent change over time we saw on repeat imaging may suggest a novel role for CMR in monitoring progression of the condition or response to therapy.

Additional imaging investigations that were not used in our case series, but that may have a role in the diagnosis and management of cardiac sarcoidosis, include positron emission tomography (PET) and radionuclide scintigraphy. Whole-body PET using the fluorodeoxyglucose (18F-FDG) isotope allows the detection of occult organ involvement. Such a finding provides strong support for the diagnosis of cardiac sarcoidosis in a patient without prior evidence of extra-cardiac disease. It also allows diagnostic tissue samples to be obtained. 18F-FDG uptake within the lung and pulmonary lymph nodes has been demonstrated to correlate with histological features of disease activity and may have similar utility when imaging the myocardium. Resting perfusion studies with Technetium-99m (99mTc) and Thallium-201 (201Tl) demonstrate reduced uptake in patients with cardiac sarcoidosis with sensitivities of 65% and 46% respectively. It is likely that these areas correspond to regions of irreversible fibrotic replacement of myocardium. In contrast, the tracer Gallium-67 (67Ga) appears to identify regions of disease activity and ongoing inflammation and may in turn provide similar information to CMR and PET imaging that guides the use of immunosuppressive therapies and allows monitoring of response to treatment. We propose a diagnostic pathway incorporating these imaging modalities for patients with suspected cardiac sarcoidosis (Fig. 1).

The ability to identify cases sooner raises hopes that early institution of directed therapy may modify the natural history of the condition. To date, the only available data arise from retrospective observational studies of glucocorticoid steroids. A recent review suggests there may be some benefit to this treatment when begun before severe cardiac dysfunction has arisen although this remains uncertain. There is even less information available on the use of alternative immunosuppressive agents, such as azathioprine. With regards to treatment efficacy, we identified a correlation between immunosuppression and normalisation of biochemical abnormalities, specifically ACE and cardiac troponin levels. Unfortunately, the clinical significance of this finding remains unclear.

Finally, our mortality was much lower than previously reported. This may be due to detection of disease at an earlier stage or with less severe cardiac involvement by having a high index of suspicion combined with improved diagnostic techniques especially CMR. Also, it is hoped that immunosuppression and increased utilisation of specific therapies, such as implantable cardiac devices, have favourably affected outcomes. Alternatively, it may simply demonstrate the diverse nature of this condition or over-diagnosis.

Study limitations

This report was retrospective and therefore is subject to the inherent biases in data recording and retrieval that arise from investigations of this nature. We report on a small number of patients in a single centre, and our findings may not be able to be generalised to the wider population. The patients were typically referred for assessment of specific symptoms deemed potentially cardiac in origin so we can offer little to guide the management of subclinical cardiac sarcoidosis.

Likely, the greatest limitation of our investigation relates to diagnostic uncertainty. A definitive diagnosis has traditionally required histological confirmation, but many studies have shown endomyocardial biopsies to have a sensitivity in the range of only 19–30%. We chose to include patients felt on the balance of evidence to have a diagnosis of cardiac sarcoidosis and exclude other cases where the diagnosis was only considered a possibility. Conversely, we did not require strict adherence to the Japanese diagnostic guidelines and did not pursue histological confirmation of the diagnosis as vigorously as other groups. This may have resulted in misclassification of patients, but alternatively, perhaps reflects real-world practice and the widespread understanding that endomyocardial biopsies have significant drawbacks both in terms of diagnostic sensitivity and potential hazard of acquisition.

Conclusions

Cardiac sarcoidosis is a rare but important cause of cardiac dysfunction, with a variable presentation and can be overlooked. A high index of suspicion should be
maintained in young patients presenting with unexplained heart block, myocardial dysfunction or ventricular arrhythmias. We found cardiac MRI contributed significantly to our identification of the condition and that thoracic CT imaging was useful in identifying concomitant extra-cardiac involvement. It seems likely that greater use of advanced imaging techniques will result in increasing recognition of this diagnosis in the future. Conversely, we found that ACE levels and troponin were often normal and much less helpful in diagnosis. Most patients were treated with immunosuppression and cardiac device therapy. With follow up of 4.8 years, we observed a mortality of 11%, less than in previous reports.

Finally, we propose a diagnostic and therapeutic pathway for patients with suspected cardiac sarcoidosis (Fig. 1).

References


4 Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with...
Dose adjustment guidelines for medications in patients with renal impairment: how consistent are drug information sources?

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Key words
renal impairment, dosage adjustment, drug prescribing, guideline, kidney disease.

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Abstract

Background: It is known that patients with renal disease are often administered inappropriate dosages of drugs. A lack of quantitative data in the available drug information sources and inconsistency in dosing information may augment the problem of dosing error.

Aims: To determine the concordance among five drug information sources regarding the dosing recommendations provided for drugs considered problematic in patients with renal impairment and to determine the consistency among the sources regarding the definition of renal impairment and categorisation of chronic kidney disease.

Methods: Five standard drug information sources were reviewed for 61 drugs recommended to be used with caution in renal impairment. Information on recommendations for dosage adjustment in renal impairment was extracted and analysed. Further, the definition and classification of renal impairment were recorded. The recommendation for each drug was coded into six different categories and the intersource reliability was calculated.

Results: Only slight agreement was observed among the sources (Fleiss Kappa: 0.3). Qualitative data were not well defined, and there was a lack of consistency in quantitative values. Some drugs marked as contraindicated in one source were not mentioned as such in others. Also, drugs considered as not requiring dosage adjustment in one source had explicit recommendations in other sources. The definition and classification of renal impairment differed among the five information sources.

Conclusions: There should be an evidence-based approach to drug dosage adjustment in order to bring uniformity to the recommendations. Regular updating of the content of the drug information sources is also important.

Introduction

Chronic kidney disease (CKD) is a long-term health condition where a person has reduced renal function, with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m2, lasting for 3 months or more. The prevalence of CKD increases disproportionally in older people because of age-related physiological changes in renal function, alongside the increasing prevalence of other conditions such as diabetes and cardiovascular disease. Impaired renal function can have pronounced effects on the pharmacokinetics of many drugs as a result of alterations in glomerular filtration, tubular secretion, reabsorption or metabolism. Therefore, there is an increased risk of drug-related problems such as the use of contraindicated drugs and inappropriate doses, with potential adverse outcomes. It is essential to select the proper drug and individualise the dosage in order to avoid the occurrence of adverse events. Previous studies have reported that 20–67% of prescriptions for patients with impaired renal function contain errors. The asymptomatic nature and opportunistic diagnosis of CKD are reasons for the higher prevalence of inappropriate prescribing. Other contributing factors reported include prescribers’ poor knowledge of medications requiring dosage adjustment, the presence of renal impairment being overlooked by prescribers, underestimation of potential adverse events, and the lack of...
evidence-based data to guide prescribers on precautions and dosage adjustments.\textsuperscript{13-17} Moreover, a lack of quantitative data in the available drug information sources, and contradiction and inconsistency in dosing information may augment the problem of dosing error.\textsuperscript{18}

In Australia, the Australian Medicines Handbook (AMH)\textsuperscript{19} or the product information provide recommendations for dosage adjustment in renal impairment. Other international resources commonly accessible include the British National Formulary (BNF)\textsuperscript{20} and the American Hospital Formulary System (AHFS).\textsuperscript{21} However, despite their availability, significant practice gaps have been reported in prescribing for patients with renal impairment.\textsuperscript{22}

The purpose of this study was to compare systematically the recommendations for dosage adjustment in renal impairment among different drug information resources. We consulted the AMH (2012), Monthly Index of Medical Specialties (MIMS; 2012),\textsuperscript{23} BNF (2012), AHFS (2012), and a specialised text, Drug Prescribing in Renal Failure (DPRF; 2007),\textsuperscript{24} for a range of drugs that is known to be problematic when used in patients with renal impairment. The specific objective was to determine the consistency among the sources in dosing recommendations provided for individual drugs and in the definition of renal impairment and categorisation of CKD.

\section*{Methods}

This systematic comparison included data extracted for 61 drugs recommended as to be used with caution in patients with renal impairment by the Department of Veterans’ Affairs, Australia (Appendix 1).\textsuperscript{25} Recommendations for dose modification in renal impairment for each of the 61 drugs were extracted from the five sources. When a drug had more than one brand available in MIMS, only one brand was chosen randomly for analysis. Data extraction also included the definitions and categorisation of renal impairment in each of the five sources. One researcher (AK) extracted the data, which was reviewed independently by another researcher (RC).

The definitions and categorisation of renal impairment reported in each of the five sources were compared with to determine consistency. The recommendations for dose modification extracted from the five sources were allocated into six categories using an adaptation of the categorisation described by Vidal \textit{et al.} as follows.\textsuperscript{18}

1 \textbf{Contraindicated (CI):} This category included drugs that were recommended to be avoided in renal impairment of any severity. For example, the AHFS recommended that ‘metformin alone or in fixed combination with other drugs is contraindicated in renal impairment’.

2 Missing (M): This category included drugs that were not included in the information source. For example, AHFS contained no information on vildagliptin and strontium ranelate.

3 \textbf{Numerical recommendations (N):}• Dose modification is recommended based on creatinine clearance (CrCl) calculated by Cockcroft-Gault (CG) formula\textsuperscript{26} or eGFR/serum creatinine (SCr) value. For example, AMH recommended a maximum daily dose of 50 mg for sitagliptin in patients with CrCl between 30 and 50 mL/min and 25 mg for patients with CrCl of less than 30 mL/min.
• Dose modification based on CrCl/eGFR/SCr is not mentioned, but there is a clear recommendation to avoid the drug below a certain range of CrCl/eGFR/SCr value. For example, AMH recommended teriparatide to be avoided in patients having a CrCl below 30 mL/min.

4 \textbf{Non-numerical recommendations (NN):}• Recommendations that were ambiguous. For example, the recommendation for metoclopramide in the BNF was to avoid or use small doses in severe renal impairment.
• Did not mention the eGFR/CrCl value/severity of renal impairment for which the drug had to be avoided or reduced. For example, the recommendation for topiramate in AMH included ‘reduced maintenance dose and longer interval between dose adjustments may be needed in renal impairment as it takes longer to reach steady state concentrations’. Further, phrases like ‘avoid in severe impairment’ in MIMS and AHFS were considered as non-numeric recommendations as these sources did not predefine ‘severe renal impairment’. However, if these sources mentioned the CrCl/eGFR range next to the severity of renal impairment, then such recommendations were considered to be numerical recommendations.
• \textit{Use with caution.} The drug information sources mentioned one of the following statements but failed to give the specific recommendation for dose adjustment based on the CrCl/eGFR/SCr value: ‘careful monitoring of dose is required’, ‘monitor the drug serum concentration’ and ‘monitor for side effects’. For example, AHFS recommended that ‘particular attention to close monitoring of methotrexate is recommended for patients with renal impairment’.
• Did not specify the required dose for the particular stage of renal impairment. For example, the recommendation for enoxaparin in BNF was ‘risk of bleeding increased, reduce dose if eGFR less than 30 mL/min/1.73 m\textsuperscript{2} – consult product literature for detail’.

5 \textbf{No advice mentioned (X):} The drug monograph was present in the information source, but there was no information on its use in patients with renal impairment. For example, the monograph for vardenafil in
Table 1  Category of dosage recommendations for 61 drugs according to five information sources

<table>
<thead>
<tr>
<th>Category</th>
<th>AMH</th>
<th>MIMS</th>
<th>BNF</th>
<th>AHFS</th>
<th>DPRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraindicated (CI)</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Missing (M)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>Numeric (N)</td>
<td>48</td>
<td>41</td>
<td>47</td>
<td>37</td>
<td>30</td>
</tr>
<tr>
<td>Non-numeric (NN)</td>
<td>9</td>
<td>17</td>
<td>12</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>No advice (X)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Not required (Y)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Total drugs</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>61</td>
</tr>
</tbody>
</table>

AMH contained no information regarding dose adjustment in patients with renal impairment.

6 Dosage adjustment not required (Y): The information source advised to give the normal drug dose in renal impairment. For example, the DPRF recommended that dose adjustment for bupropion is not required.

For the purpose of analysis, the six categories of recommendations were coded numerically to assign comparable values with CI = 1, M = 2, N = 3, NN = 4, X = 5 and Y = 6 respectively. The concordance in dosing recommendation for all 61 drugs among the different sources was calculated using Fleiss Kappa ($\kappa$). The concordance was determined in two approaches using REnCal, an intercoder reliability web service. In the first approach, concordance was calculated for the 34 drugs that had information in all five sources, excluding drugs that were missing from one or more sources. In the second analytical approach, the DPRF book was excluded, as it was an older publication, and the concordance was determined for the 54 drugs included in all the remaining four information sources.

Results

All the five information sources provided recommendations in quantitative terms for the majority of drugs examined in the study (Table 1). AMH provided precise recommendations (N and CI) for the highest number of drugs ($n = 51$), followed by BNF ($n = 48$). Monographs for 44% of the drugs ($n = 27$) were missing from DPRF. However, DPRF generally provided the clearest information for the other drugs. The first analysis showed only slight agreement ($\kappa = 0.3$) among the five information sources. A moderate agreement ($\kappa = 0.4$) was observed in the second analysis when the DPRF was excluded. When assessing the individual categories of drugs, the least agreement was found among the recommendations for gliptins ($\kappa = 0.19$), followed by genitourinary drugs ($\kappa = 0.05$), angiotensin-converting enzyme (ACE) inhibitors ($\kappa = -0.03$), oral hypoglycaemics (metformin, glimepiride, glibenclamide) ($\kappa = 0.04$), musculoskeletal drugs ($\kappa = 0.15$), psychotropic drugs ($\kappa = 0.19$) and neurological drugs ($\kappa = 0.19$).

There was marked variation among the information sources in how they presented the contraindicated drugs. In various instances, drugs marked as contraindicated in one source were not mentioned as such in others (Table 2). AHFS recommended avoiding metformin use even in mild renal impairment. However, the avoidance range for metformin according to AMH was CrCl $< 30$ mL/min; for MIMS, it was CrCl $< 60$ mL/min; for BNF, it was eGFR $< 30$ mL/min; and for DPRF, it was GFR $< 10$ mL/min. AMH and AHFS considered glibenclamide to be contraindicated in renal impairment, while DPRF recommended using normal dose in even severe renal impairment (GFR $< 10$ mL/min). AMH considered codeine as contraindicated, whereas three information sources (MIMS, AHFS and BNF) did not specify this contraindication, and interestingly, DPRF recommended using half of the normal dose even if GFR $< 10$ mL/min. AMH and AHFS considered hydromorphone to be contraindicated in renal impairment, while DPRF recommended normal dose if GFR $> 60$ mL/min. AMH and AHFS considered codeine as contraindicated, whereas three information sources (MIMS, AHFS and BNF) did not specify this contraindication, and interestingly, DPRF recommended using half of the normal dose even if GFR $< 10$ mL/min. AMH and AHFS considered codeine as contraindicated, whereas three information sources (MIMS, AHFS and BNF) did not specify this contraindication, and interestingly, DPRF recommended using half of the normal dose even if GFR $< 10$ mL/min. AMH and BNF provided quantitative recommendations. Monographs for both vardenafil and teriparatide were missing from DPRF.
Apart from the dissimilarity in the categories of recommendation, disparity was found among the information sources in how they provided the quantitative recommendation. The dose reduction and dosing frequency advised for the particular drugs in the varying severities of renal impairment contrasted among the sources (Table 3). On examining the individual information sources, it was found that some of the recommendations were contradictory. For instance, with regard to famotidine in AHFS, this information source suggested using one-half the normal dosage or prolonging the dosing interval to 36–48 h according to the patient’s clinical response in moderate renal impairment (CrCl < 50 mL/min) or severe impairment (CrCl < 10 mL/min). On the other hand, the same information source advised to use one-half the usual adult dosage in adults with CrCl of 30–60 mL/min/1.48 m² of body surface area and use one-fourth the usual adult dosage in patients with CrCl < 30 mL/min/1.48 m². Other examples were: metoclopramide in BNF, ‘avoid or use small dose in severe renal impairment’; and bisoprolol in MIMS, ‘no dosage adjustment is required in patients with impairment of the kidney because of excretion equally by both liver and kidney. Nevertheless, caution is advised’ (Table 4).

CrCl was the most common index to direct the dosage adjustment in the information sources. AMH and DPRF recommended dose adjustment based on CrCl calculated by the CG formula. However, BNF provided recommendations based on eGFR calculated by the modification of diet in renal disease (MDRD) formula.31 The renal function quantification methods varied among the drug monographs within AHFS and MIMS. For the majority of drugs, dosage adjustment was based on the CG formula, and for some drugs, the MDRD formula was used, especially when referring to manufacturers’ recommendations.

The definition and classification of renal impairment differed in all five sources. The classification for renal impairment in BNF categorised the renal function into five different stages; this complies with the definitions by the British Renal Association.32 AMH had its own system of classification of renal impairment designed solely to aid the drug dosage adjustment; this differs from the Caring Australians with Renal Impairment guidelines.33 DPRF defined renal impairment based on absolute GFR and divided them into three categories; this does not correspond to any standard classification system. MIMS and AHFS did not provide clear definitions of categories of renal impairment, and terms like mild, moderate and severe impairment were used without definition. Furthermore, various terms were used for dosage recommendation in the information sources without proper definition; these included a clinically significant degree of renal impairment, rapidly deteriorating renal function and substantial impairment of renal excretory function.

**Discussion**

There was considerable variation between the information sources in recommendations for the use and dosing of drugs in patients with renal impairment. Vidal et al. similarly concluded that there was poor consistency among four information sources: BNF, Martindale, AHFS and DPRF for the renal dosing of 100 drugs used commonly in the hospital setting.39 However, their study had some limitations, particularly relating to the method of selecting the most commonly prescribed drugs within a hospital environment rather than focusing on high-risk drugs excreted primarily through the renal route.34,35 Therefore, we compared the drug information sources based on their dosing recommendations for the drugs that have most potential for inappropriate prescribing in kidney disease.

The results of our study illustrate that there is a lack of quantitative recommendations in the various information sources to guide health professionals reliably on appropriate prescribing to minimise adverse outcomes in patients with renal impairment. It is recognised that it is unrealistic to quantify the appropriate dose for some drugs with large pharmacodynamic variability – for instance, ACE inhibitors and β-blockers, whose dosage adjustment should not be based solely on pharmacokinetic parameters but clinical factors like blood pressure and heart rate as well. However, clear quantitative information in one source and unclear information in other information sources, such as ‘increase dosing interval’ or ‘seek specialist advice in severe impairment’, will complicate the prescribing decision.

One of the reasons for the lack of robust dosing information could be the paucity of large population-based studies on dose adjustment in renal impairment. Another contributing factor could be the practice of the drug regulatory authorities that focuses mainly on clinical trials determining the maximum tolerated dosage in healthy, young individuals.35 Keeping aside the fact that few studies are available that determine the correct dose in renal impairment, the dissimilarity between standard information sources regarding the reported availability of clinical study data was remarkable; drugs for which one information source mentioned a lack of clinical study data on dose adjustment, other sources provided clear quantitative recommendations.

It is well understood that contraindications and cautions are seldom absolute, but the differing recommendations create ambiguity and uncertainty, and can
## Table 3

Some examples of discrepancies in quantitative recommendations among the information sources

<table>
<thead>
<tr>
<th>Drugs/Dose for normal renal function</th>
<th>AMH</th>
<th>MIMS</th>
<th>BNF</th>
<th>AHFS</th>
<th>DPRF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CrCl (mL/min)</td>
<td>Dose (max/day)</td>
<td>CrCl (mL/min)</td>
<td>Dose (max/day)</td>
<td>eGFR (mL/min/1.73 m²)</td>
</tr>
<tr>
<td>Metformin 500–850 mg bd</td>
<td>60–90</td>
<td>2 g</td>
<td>&lt;60</td>
<td>Avoid</td>
<td>&lt;45</td>
</tr>
<tr>
<td></td>
<td>30–60</td>
<td>1 g</td>
<td>&lt;60</td>
<td>Avoid</td>
<td>&lt;30</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>Avoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glibenclamide 1.25–20 mg q24h</td>
<td>RI</td>
<td>Avoid</td>
<td>Severe RI</td>
<td>Avoid</td>
<td>Use with care in mild-to-moderate RI</td>
</tr>
<tr>
<td>Sitagliptin 100 mg OD</td>
<td>30–50</td>
<td>50 mg</td>
<td>&lt;60</td>
<td>Avoid</td>
<td>30–50</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>25 mg</td>
<td>&lt;60</td>
<td>Avoid</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Saxagliptin 5 mg OD</td>
<td>&lt;50</td>
<td>2.5 mg</td>
<td>&gt;50</td>
<td>5 mg</td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td>30–50</td>
<td>5 mg</td>
<td>&lt;60</td>
<td>Avoid</td>
<td>30–50</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>Avoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide 20 micrograms OD</td>
<td>&lt;30</td>
<td>Avoid</td>
<td>Dosage adjustment not required</td>
<td>Caution in moderate impairment; avoid if severe RI</td>
<td>No advice for dosage adjustment in RI</td>
</tr>
<tr>
<td>Colchicine Acute 2 mg, then 0.5–1 mg q24h</td>
<td>&lt;30</td>
<td>Avoid in acute attack</td>
<td>10–50</td>
<td>Reduce dose or increase dose interval</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Acute 0.5 mg q6h chronic: 0.5–1 mg q24h</td>
<td>&lt;80</td>
<td>Avoid in acute attack</td>
<td>&lt;10</td>
<td>Avoid</td>
<td>10–50</td>
</tr>
<tr>
<td>Bupropion 150–300 mg OD</td>
<td>RI: 150 mg</td>
<td>Use reduced dose and/or frequency</td>
<td>RI: 150 mg</td>
<td>Use with caution in RI</td>
<td>No need for dosage adjustment</td>
</tr>
<tr>
<td>Duloxetine 30–60 mg OD</td>
<td>&lt;30</td>
<td>30 mg</td>
<td>&lt;30</td>
<td>30 mg</td>
<td>&lt;30</td>
</tr>
</tbody>
</table>

AHFS, American Hospital Formulary System; AMH, Australian Medicines Handbook; BNF, British National Formulary; CrCl, creatinine clearance; DPRF, Drug Prescribing in Renal Failure; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; ID, initial dose; MD, maintenance dose; MIMS, Monthly Index of Medical Specialties; NA, not available; ND, normal dose; NR, not required; RI, renal impairment.
Table 4  Examples of ambiguous recommendations in information sources

<table>
<thead>
<tr>
<th>Drugs</th>
<th>AMH</th>
<th>MIMS</th>
<th>BNF</th>
<th>AHFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>Morphin: use an alternative opioid (or reduce dose if CrCl &lt;50 mL/min). Hydromorphone: reduce dose in renal impairment and monitor for adverse effects.</td>
<td>Tramadol: avoid use or reduce dose. Codeine: use with caution. Oxycodone: dosage should be reduced and adjusted according to the clinical situation.</td>
<td>Morphin: avoid use or reduce dose. Codeine: avoid use or reduce dose. Hydromorphone: avoid use or reduce dose.</td>
<td>Morphin: use with caution. Codeine: care should be exercised. Hydromorphone: reduce initial dose. Oxycodone: reduce dose and adjust according to the clinical situation. Baclofen: may be necessary to reduce either oral or intrathecal dosage in renal impairment.</td>
</tr>
<tr>
<td>Neurological</td>
<td>Baclofen: 5 mg initially; titrate dose cautiously according to response. Topiramate: reduce maintenance dose. Levetiracetam: reduce dose in renal impairment.</td>
<td>Topiramate: renal clearance is decreased in renal impairment.</td>
<td>Topiramate: use with caution if eGFR less than 60 mL/min/1.73 m².</td>
<td>—</td>
</tr>
<tr>
<td>Blood disorders</td>
<td>Enoxaparin: use with caution in renal impairment reduce dose if CrCl &lt;30 mL/min.</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Methotrexate: particular attention to close monitoring is recommended.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Sotalol: increase dosing interval. Seek specialist advice for dose adjustment in severe impairment. Bisoprolol: no dose reduction required up to 10 mg daily in renal impairment</td>
<td>Digoxin: use with caution in renal impairment. Captopril: initial daily dosage should be reduced Bisoprolol: no dosage adjustment is normally required up to the max dose of 10 mg.</td>
<td>Digoxin: reduce dose and monitor plasma digoxin concentration.</td>
<td>Candesartan: 4 or 8 mg daily in severe impairment.† Digoxin: loading doses should be conservative. Spironolactone: use with caution in renal impairment, contraindicated in rapidly deteriorating renal function, substantial impairment of renal excretory function. Glimepiride: initial dosing should be conservative.</td>
</tr>
<tr>
<td>Endocrine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Metoclopramide: initiate therapy at half of the dose in patients with clinically significant degrees of renal impairment. Ranitidine: reduce dose on severe renal impairment.</td>
<td>Metoclopramide: avoid or use small dose in severe impairment.</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

†Mild, moderate and severe impairment were not defined in the information sources. AHFS, American Hospital Formulary System; AMH, Australian Medicines Handbook; BNF, British National Formulary; CrCl, creatinine clearance; MIMS, Monthly Index of Medical Specialties.
misdirect the users or prescribers. For particular drugs, such as oral hypoglycaemics, H₂ receptor blockers, metoclopramide and many cardiovascular drugs, the information sources often did not provide explicit information for dosage adjustment, yet studies have shown that incorrect dosage adjustments are common with these categories of drugs. Guidelines for dose adjustment in renal impairment, even for drugs with a narrow therapeutic index (e.g. digoxin and lithium), were poorly mentioned in the information sources. Instead of a clear quantitative recommendation, qualitative and ambiguous terms like ‘reduce the dose’ and ‘loading dose should be conservative’ were often used.

It was found that the information sources were relatively consistent in providing recommendations for newer drugs, such as levetiracetam, memantine, paliperidone, pramipexole and pregabalin. This improved consistency could be due to the manufacturers providing more robust data for clinical use and dosage adjustment, and regulatory authorities demanding more consistent information. Clearly, regular updating of the drug information sources is necessary, along with a need for all drugs that are to be used in patients with renal dysfunction to undergo at least one pharmacokinetic study in patients with varying degrees of renal impairment prior to marketing. An emphasis should be placed on conducting and disseminating research work focused on determining the correct drug dosage based on renal function.

Uniformity in the categorisation of renal impairment would be desirable as prescribers tend to refer to more than one information source for advice on drug dose adjustment in renal impairment. Keeping in mind the new practice of automatic eGFR reporting, drug dosage recommendations based only on CrCl could be inconvenient. Recently, it was suggested that the method of calculating eGFR should be changed to the CKD Epidemiology Collaboration (CKD-EPI) formula and that all laboratories should report eGFR values as a precise figure to at least 90 mL/min/1.73 m². However, it has been recommended that the dosage adjustment for drugs with a narrow therapeutic index or excreted primarily by kidney should be guided by CrCl calculated by the CG equation. Further, in elderly or frail patients and in those with a low body mass index, CrCl is the preferred renal function quantification method. Therefore, recommendations for dose adjustment based on both CrCl and eGFR/CKD-EPI would be ideal.

Editors of secondary sources accept the difficulties in finding and compiling the relevant information for patients with renal disease on which clear dosing guidelines can be formulated. Furthermore, the value of the product information will always be limited by the regulatory process (data requirements, economics and approval delays) and the generally conservative approach by manufacturers (fear of litigation). It will always be necessary to interpret the product information and make a risk-benefit decision for individual patients. Also, while adjusting the dose in clinical practice, the prescriber needs to be confident that the pharmacokinetic parameters of the patient they are treating do not vastly differ from the population in which the renal pharmacokinetic study was undertaken.

Our study was limited to drugs used commonly in the community setting, and so excluded renally important drugs used primarily in hospital settings (e.g. aminoglycoside antibiotics). However, in light of the inconsistency in the recommendations for the 61 drugs in our study, we believe a similar result would be obtained if a greater number of renally problematic drugs were examined. Also, we acknowledge that there are other sources of drug dosing information in renal disease that might be used in practice, especially within specialist renal units. However, we have examined the information sources most commonly used by Australian general practitioners and pharmacists in the community setting.

**Conclusion**

There should be an evidence-based approach to drug dosage adjustment in renal disease to bring uniformity to the recommendations. Further, it would be beneficial to standardise the renal function quantification methods in the drug information sources. We believe that this would reduce the possibility of inappropriate dosing for patients with renal impairment.

**References**

6. Fink JC, Chertow GM. Medication errors in chronic kidney disease: one piece in
Appendix 1: Drug list used in the study

Medicines that may accumulate and require renal function monitoring

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Genitourinary</th>
<th>Blood</th>
<th>Endocrine</th>
<th>Musculoskeletal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Solifenacin</td>
<td>Dabigatran</td>
<td>Glibenclamide</td>
<td>Allopurinol</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Sildenafil</td>
<td>Enoxaparin</td>
<td>Glimepiride</td>
<td>Bispophonates</td>
</tr>
<tr>
<td>Morphine</td>
<td>Tadalafil</td>
<td>Rivaroxaban</td>
<td>Saxagliptin</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Tolvaptan</td>
<td>Vildagliptin</td>
<td>Sitagliptin</td>
<td>Strontium ranelate</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Vardenafil</td>
<td>Metformin</td>
<td>Metformin</td>
<td>Teriparatide</td>
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Source: www.veteransmates.net.au.
BRIEF COMMUNICATIONS

Embedding research in clinical practice: differences in attitudes to research participation among clinicians in a tertiary teaching hospital

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Key words
research activities, health personnel, allied health personnel, medical staff, nursing staff, paediatrics.

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Abstract
Despite a drive to increase research in healthcare settings, clinician participation in research remains infrequent. This paper describes an online survey comparing attitudes with research participation among clinicians (doctors, nurses and allied health professionals) at an Australian tertiary children’s hospital. Differences between professional groups support the existence of different professional cultures surrounding research, suggesting that multiple strategies are required to improve participation in research.

The drive for evidence-based practice has included a demand for research to be embedded within the healthcare setting. Clinicians are well placed to identify relevant research ideas and ensure translation of research into improved health outcomes. Hospitals engaged in research have been recognised to provide better patient care.¹

However, only a minority of healthcare professionals is involved in research. In Australia, 7% of the medical workforce report active involvement in research,² and 1% of nurses identify research as their primary role.³ Most Australian paediatricians assign limited time for research, with 26.7% not involved in any research.⁴ Paediatric nursing research has been presented as in crisis.⁵ Tertiary teaching hospitals therefore have a responsibility to provide leadership in conducting, supporting and supervising research.

Factors that influence clinicians’ (doctors, nurses and allied health professionals) involvement in research have been reported in various clinical settings. Common barriers include lack of time,⁶⁻¹² insufficient support⁶⁻¹⁰,¹³ and limited skills and knowledge about research,⁶⁻⁸,¹³,¹⁴ although factors influencing research participation are complex. Studies from the United States have suggested that attitudes to research participation differ between professional groups working at the same institution.¹⁰,¹⁵ At the present time, there are no equivalent Australian studies, but such studies are needed to identify appropriate strategies to improve research participation in Australian teaching hospitals.

Responding to the problem of poor research uptake at public teaching hospitals identified in the Garling report,¹⁶ a multidisciplinary working party on ‘Engaging Clinicians in Research’ was set up at The Children’s Hospital at Westmead, Sydney, NSW, Australia. Its goal was to improve research participation among clinical staff working at the hospital. This study was conceived as the first step towards this goal.

A 28-item online questionnaire was developed by the working party to identify attitudes to research participation and perceived barriers to research of the different professional groups within the hospital. Items included the demographic details of participants (age, gender, professional role and seniority), the extent of their research experience, their attitudes to research and their perceptions of their departments’ and the hospital’s attitudes to research participation and personal enablers, and barriers to research participation. A copy of the questionnaire is available on request from the authors. Twenty-four binary-option questions and four open-ended questions were used to ensure both high discriminative value and to allow participants to elaborate on their responses. Descriptive data are presented as means or proportions with 95% confidence intervals and categorical data
compared using $\chi^2$ for differences in proportions. Data were analysed using SAS (version 9.2, SAS Institute Inc., Cary, NC, USA). Ethics approval was obtained from the hospital ethics committee.

The online questionnaire was accessible from November 2009 to January 2010. One thousand, two hundred and ten clinicians (nurses, doctors and allied health professionals) working at the hospital were sent an email invitation. Strategies were used to increase recruitment, including email reminders, personal invitation, requesting department heads and nurse unit managers to promote participation, using a deadline and following up contacts.\textsuperscript{17} A targeted email invitation was resent to junior medical staff following poor response from this group (one response).

The recruitment rate was low (17%) with only 208 respondents, despite the strategies to increase recruitment. Nurses were underrepresented (30% of survey respondents; 9% of nurses) compared with doctors (36% of respondents; 25% of doctors) and allied health staff (34% of survey respondents; 34% of allied health clinicians) in our sample. Most participants worked in a clinically focused environment, with 37% identified as working in a research-focused or mixed (research-clinical) environment.

Demographic and professional details of participants are shown in Table 1. Professional groups differed significantly with a higher proportion of men in the medical group ($P < 0.0001$), more allied health participants in the younger (<30 years) age range ($P = 0.0004$) and more doctors having masters or doctorate degrees ($P = 0.0005$) than other groups. Most participants identified themselves as having research skills or experience (63%) or formal research training (66%) but as having less than 5 years of research experience (73%). Twenty-two per cent of participants reported submitting a research grant application during the previous 5 years.

Most participants reported that they enjoy participating in research (68%) and that their departments value research (66%) and have an expectation of staff to be involved in research (71%), but that support for research is inadequate. Some allied health professionals reported that research is encouraged but not expected by their departments. Most regarded participation in research to be an important part of their professional role (Fig. 1a) and as important to career progression (71% overall), although nurses (55%) less so than doctors (84%) or allied health participants (71%) ($P = 0.004$). Doctors (59%) were more likely to report a recognised route to become involved in research than allied health (43%) and nursing staff (32%) ($P = 0.006$).

Professional groups were similarly motivated to be involved in clinical research instigated by others (Fig. 1b,c), but nurses reported less motivation to conduct their own research ($P = 0.016$). Nurses also reported fewer opportunities to be involved in clinical research (48%) than doctors (68%) or allied health professionals (59%) ($P = 0.04$).

Most participants reported inadequate time (73%) for research and inadequate resources or infrastructure support (50%). In an open question asking about barriers to research involvement, four themes dominated the responses: lack of time, lack of personnel, lack of departmental/hospital support and lack of funding with all three professional groups identifying the pressures of clinical work and the lack of protected research time as the major barriers. Examples of comments given include ‘. . . things would be a lot easier with more resources/infrastructure and more protected time for research’ (a doctor) and ‘There seems to be very little support or

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Doctors ($n = 76$)</th>
<th>Nurses ($n = 62$)</th>
<th>Allied health ($n = 70$)</th>
<th>All respondents ($n = 208$)</th>
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<td>Role/discipline (n)</td>
<td>SMO 25 RN 13 PT 15</td>
<td>JMO 51 CNS 33 OT 13</td>
<td>NM 11 SW 11</td>
<td>Other 5 SP 4 Other 27</td>
</tr>
<tr>
<td>Males (%)</td>
<td>39 (51)*</td>
<td>5 (8)</td>
<td>6 (9)</td>
<td>50 (24)</td>
</tr>
<tr>
<td>Age group (%)</td>
<td>&lt;30 years</td>
<td>9 (12)</td>
<td>8 (13)</td>
<td>25 (36)*</td>
</tr>
<tr>
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<td>30–50 years</td>
<td>60 (79)</td>
<td>41 (66)</td>
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<td>&gt;50 years</td>
<td>7 (9)</td>
<td>13 (21)</td>
<td>9 (13)</td>
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<td>Research experience (masters or PhD)</td>
<td>35 (46)*</td>
<td>18 (29)</td>
<td>17 (25)</td>
<td>70 (34)</td>
</tr>
</tbody>
</table>

*P < 0.001. CNS, clinical nurse specialist (including clinical nurse consultants and clinical nurse educators); JMO, junior medical officer; NM, nurse manager (including nurse unit manager); OT, occupational therapist; PT, physiotherapist; RN, registered nurse; SMO, senior medical officer; SP, speech pathologist; SW, social worker.
Responses to an open question asking for suggestions for improving clinician involvement in research were categorised into seven themes: protected time away from clinical load; more accessible funding; accessible education about the research process; providing mentors who are experienced in research; developing a supportive attitude towards research within the department/hospital; and greater acknowledgement of staff contribution to research and fostering collaboration across departments. Examples of comments given include ‘Demystifying of research for staff – many are “scared” of research, believing that it must be very complicated and time consuming’ (an allied health professional) and ‘Multidisciplinary approach should be employed. Emails sent out to invite interested parties . . . ’ (a nurse).

This is the first study to compare the attitudes to research participation of clinicians from different professions working in an Australian tertiary paediatric hospital. The high proportion of respondents with research experience or working in research-focused environments in our survey suggests that our results reflect the responses of clinicians who are more likely to be interested in research and may not be generalisable to the population of clinicians working in the hospital. The low response rate suggests general apathy about research (by non-participants) and highlights the plight of conducting research in a tertiary teaching hospital. Some groups may have had less access to email because of working patterns, which may account in part for the low response rates among nurses. However, the comparison of attitudes to research among different professional groups of clinicians interested in research is informative.

Our results support the existence of different professional cultures concerning research participation in our institution. The perception of nurses that research is less important for career progression and not part of their professional role has been reported previously. Studies have also suggested that a nursing culture has persisted that identifies direct patient contact as its only core business. This combined with time pressures created by clinical workloads and the short-term goal focus of healthcare management have resulted in research being perceived as a luxury or imposition. The increased opportunity and recognised routes for research participation reported by doctors also suggest that, at least at this institution, it is easier for doctors to be involved in research compared with other groups. This difference may also account for the reduced motivation to lead research projects reported by nurses.

The barriers to research participation reported by all three professions (lack of time, resources, infrastructure

**Figure 1** (a) Importance of clinical research participation as part of job/role by profession. (b) Motivation to conduct own research by profession. (c) Importance of involvement in clinical research by someone else by profession: Medical (n = 76); Nursing (n = 62); Allied health (n = 70); All groups (n = 208).
and institutional attitudes) are not new.6–14 Studies have suggested that some clinicians have limited interest in research;3,12 do not see research as part of their professional role10–11,14 or see research as irrelevant to clinical work.4,9,11 This was not demonstrated in our cohort, likely because of bias in our sample. Some have suggested that the true reasons for clinicians’ ambivalence to research participation are hidden beneath more peer-accepted responses provided in quantitative studies, such as ours,11,12 and we have since conducted qualitative methods research (focus groups) to explore this.

Our clinicians identified potential interventions to improve research participation, including protected time, protected resources, research skills training and mentorship and collaboration between teams, similar to other studies.7,14 Facilitative interventions to increase research capacity in nurses (e.g. research courses, assistance for grant applications and paper writing) are often well received, but evidence that they increase research awareness and output is limited.19 Protected time for research would require a significant change in working practices for most clinicians. Whether recent government papers16 produce enough political pressure to effect this change is yet to be seen.

The differences between professional groups identified in our study, and awareness of the different working environments of the health professionals surveyed suggest that multiple strategies will be required with a focus on cultural changes to research participation if the goal of increasing clinician engagement in research in a tertiary teaching hospital is to be achieved.

Acknowledgements

The authors thank members of the Engaging Clinicians in Research Working Party (The Children’s Hospital at Westmead) (Peter Van Asperen, Paul Robinson, Melanie Wong, Margaret Kelly, Yashwant Sinha, Jonathan Craig, Nicholas Wood, Malay Rana, Mary McCaskill, Hiran Selvadurai, Stuart Dorney, Alison Jones, Tom Pitham and Claudia Green) for their assistance with the design of the questionnaire; Joyce Murphy (Service Improvement Unit, The Children’s Hospital at Westmead) for help with the questionnaire and data collection and Liz Barnes (The Children’s Hospital at Westmead and University of Sydney) for her assistance with statistical analysis.

References

Successful treatment of Erdheim–Chester disease with combination of interleukin-1-targeting drugs and high-dose glucocorticoids

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Key words
interleukin-1 receptor antagonist, Anakinra, Erdheim–Chester disease, treatment, histiocytosis.

Abstract
Erdheim–Chester disease (ECD) is a rare histiocytic disorder. We report a case of a 45-year-old male ECD patient with severe clinical manifestation (urinary obstruction due to retroperitoneal mass with hydrenephrosis, involvement of long bones) and central nervous system involvement (hemiparesis, aphasia and diabetes insipidus). Diagnosis was confirmed by typical clinical, radiological and histological findings. Under immunosuppressive therapy with prednisolone and interleukin-1A receptor antagonist (Anakinra, Kineret, Swedish Orphan Biovitrum AB, Stockholm, Sweden), a rapid improvement of the patients’ symptoms and condition was observed. This is the first report of a successful combination therapy of Anakinra and glucocorticoids. Furthermore, current literature about ECD and treatment options are discussed.

Erdheim–Chester disease (ECD) is a rare histiocytic disorder first described by Jakob Erdheim and William Chester in 1930.¹ There have been merely several hundred cases reported until today. It is also known as polyostotic sclerosing histiocytosis because of the typical multifocal osteosclerotic lesions of the long bones. In tissue biopsy foamy histiocytes immunoreactive for macrophage markers (CD 68, CD 14, CD 163) but not for Langerhans cell histiocytosis, markers are characteristic.² There is a high variability in clinical presentation depending on affected organs. In retrospective case series, the following organ involvement has been described: long bones (95%), maxillary sinus, large vessels and retroperitoneum (59% each), heart (57%), lungs (46%), central nervous system (CNS) (41%), skin (27%), and of pituitary gland and orbit (22% each).³

Here we present the case of a 45-year-old male patient with retroperitoneal mass, involvement of CNS, exophthalmos and diabetes insipidus caused by ECD.

In February 2012, the patient noticed severe pain in the flank region. As part of further investigation, a bilateral high-grade hydrenephrosis caused by a retroperitoneal mass with obstruction of both ureters was diagnosed, and double-J catheters for urinary drainage were installed. Tissue from the retroperitoneal mass was obtained by computed tomography (CT)-guided biopsy for pathological examination, which turned out as fibrohistiocytic lesion. Although the histological result was not typical for the presence of idiopathic retroperitoneal fibrosis, immunosuppressive therapy with prednisolone was started. With this treatment, the patient was free of symptoms for the next months.

In April 2012, the patient noticed severe pain in the kidney region. Acute renal failure caused by post-renal urinary obstruction was diagnosed and treated by changing the double-J catheters. After removal of the urinary obstruction, the patient’s symptoms improved and his kidney function returned to normal. During the hospital stay, a progressive increase in blood pressure with recurrent hypertensive crisis was observed. Furthermore, the clinical examination revealed an incomplete left hemiparesis and aphasia. With detection of lacunar lesions of the basal ganglia and cerebellar lesions through cranial CT, ischaemic stroke was suspected. In the further course, the patient developed again a bilateral pyelonephritis with hydrenephrosis. After detection of a secondary urinary infection, antibiotic therapy was initiated and
the double-J catheters were changed. Despite decreasing levels of inflammatory laboratory markers, the patient’s condition worsened continuously. In addition to neurological symptoms, the patient developed fatigue, loss of appetite, nausea, vomiting, headache and vertigo. An increase of blood pressure and inflammation levels was recognised. Within a few days, the patient presented with a paraparesis, progress of aphasia and oral sensory disturbances. At the time of admission to our department (and diagnosis of ECD), the following findings were observed: the physical examination showed a severely ill patient in strongly reduced general condition. There was an exophthalmos of the right eye. The neurological examination revealed a paraparesis of the legs with a positive Babinski sign and a weakness of both arms. Heart rate showed a sinus tachycardia (116/min) whereas examination of lungs and abdomen did not reveal any pathological findings.

In the laboratory testing, signs of inflammation with an elevated C-reactive protein (CRP) level (55 mg/L; upper limit of normal (ULN): 5 mg/L) and white blood cells (WBC) (12.3/nl; ULN: 10/nl), increased fibrinogen (652 mg/dl; ULN: 350 mg/dl) and increased soluble interleukin (IL)-2 receptor (1593 U/mL; ULN: 623 U/mL) were found. Procalcitonin, autoantibodies, vasculitis diagnostics, hepatitis and HIV screening showed no relevant pathological findings. In the endocrine diagnostics corticotrope, thyrotrope and somatotrope insufficiency was excluded. A vitamin D deficiency with normal parathyroid hormone was found.

For radiological investigation, cranial, thoracic and abdominal CT was performed. The cranial CT showed lesions of the basal ganglia and the cerebellum. Around both kidneys and the proximal ureter, a poorly defined retroperitoneal mass was seen. The perirenal mass showed a ‘hairy kidney’ aspect, typical for ECD, as presented in Figure 1.

After exclusion of vasculitis, infectious or malignant aetiology of the symptoms ECD was diagnosed, with the involvement of long bones, pituitary gland (diabetes insipidus), neurological disorders and retroperitoneal fibrosis. The histopathological evaluation of the biopsy of the retroperitoneal mass showed a fibrohistiocytic lesion as seen in reactive inflammatory response. Similar results from biopsies of retroperitoneal masses in ECD have been described before in the literature.

An immunosuppressive therapy with Anakinra (Kineret, Swedish Orphan Biovitrum AB, Stockholm, Sweden) 100 mg/day and prednisolone 100 mg/day was initiated. After a few days, the clinical condition of the patient improved significantly. Nausea, dizziness, headache and vomiting disappeared almost completely. The neurological symptoms of aphasia and motoric deficits of the arms improved. In parallel, there was a rapid decrease of CRP, WBC and fibrinogen.

However, after initiation of treatment a post-renal kidney failure with Gram-negative urosepsis (with Escherichia coli in urine) occurred again. Under antibiotic therapy, the infection was controlled and the patient could be transferred to a rehabilitation facility with persistent paraparesis.

Today, 5 months after diagnosis of ECD, the patient is still on therapy with Anakinra 100 mg s.c. once daily, resulting in a stable condition with residual paraparesis of his legs. Prednisolone was tapered weekly reaching 20 mg per day. At the last outpatient visit, daily prednisolone dose was still 20 mg; however, further dose reduction is planned. For prophylaxis of Pneumocystis carinii pneumonia, cotrimoxazol 960 mg was given twice weekly.

Confiriming the diagnosis of ECD is a medical challenge. ECD might have been overlooked in the past; in the last 10 years, the number of new reported cases has increased. The diagnosis of ECD must be considered when typical clinical features, imaging (e.g. ‘hairy kidney’) and histological findings (as fibrohistiocytic lesions) occur. To confirm diagnosis, biopsy of an osteosclerotic bone lesion can be helpful. Unfortunately, complete histological confirmation of the diagnosis is often impossible. The histological diagnosis should exclude a malignant or infectious origin and confirm the diagnosis by demonstrating characteristic histiocytes. The biopsy of the retroperitoneal mass often reveals a reactive non-specific inflammatory response. The course of disease in ECD is highly variable. The involvement of the CNS especially appeared as a predictor for a severe course with high mortality. The most common treatment option of ECD is pegylated α-interferon (IFN-α), which is reported to reduce morbidity and mortality. Other treatment options like...
glucocorticoids, systemic chemotherapy or radiotherapy have been described. A successful treatment of ECD with Anakinra monotherapy was first described in 2010 by Aouba et al. The rationale for Anakinra therapy is based on increased expression of IL-1β and IL-18 in monocytes in ECD patients, overlapping mechanisms of action with interferon and the known effectiveness and safety of Anakinra therapy in other autoimmune diseases. To date, a total of five cases treated with Anakinra monotherapy was reported. Due to the severity of the disease in our patient and a suspected depressive disorder, we did not use pegylated IFN-α but started a combination therapy with high doses of glucocorticoids and Anakinra. In our patient, 24–48 h after initiation of therapy, a reduction of headache, nausea, vomiting, dizziness and a marked decrease of CRP, fibrinogen and WBC was noticed. The urosepsis was more likely associated with the urinary obstruction and hydronephrosis than to medical immunosuppression. Since today, no other infectious complications occurred in our patient under Anakinra treatment.

Normalisation of laboratory values (such as CRP), fatigue, bone pain and fever are reported during Anakinra treatment in patients with ECD. After several months of therapy, a decrease in bone lesions and retroperitoneal fibrosis was described.

In conclusion, ECD is a rare disease characterised by fibrohistiocytic lesions in different affected organs. Most common is an involvement of long bones, large vessels, retroperitoneum, lung, heart and CNS. In suspected ECD, diagnosis should be made by histological assessment. Although interferon is described as most common therapy in ECD, combination therapy with IL-1-targeting drugs and glucocorticoids can be performed safely and successfully in severe or refractory cases of ECD. Further clinical observations and studies are necessary to evaluate the efficiency and security of this therapy in all ECD patients.

References

Inadequate resuscitation documentation in older patients’ clinical case notes

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Key words
terminal care, resuscitation order, cardiopulmonary resuscitation, advance care directive, aged care.

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Abstract
This research examined the quality of resuscitation decisions documented in the clinical notes of 99 older patients within 48 h of admission. Only 34 had current documentation that was frequently inconsistent and ambiguous, leaving patients at risk of receiving inappropriate and unwanted resuscitation. Clear guidelines with community input to guide the implementation and documentation of end-of-life decisions are essential.

When an inpatient suffers a cardiopulmonary arrest, resuscitation is the default response. This resuscitation process often starts by calling for the immediate presence of a medical emergency team (MET), a group of senior doctors and nurses. Even though many inpatients are older and may be dying, this resuscitation process will commence unless there are clearly documented decisions in the clinical notes not to resuscitate the patient.

Although survival and neurological outcomes after cardiopulmonary resuscitation (CPR) have improved in recent years, inappropriate attempts may lead to unwanted medical treatments, including admission to an intensive care unit, which can be distressing for families as well as staff. The decision about the type and extent of resuscitation is a medical decision that should be made in consultation with the patient, where possible, and also with relatives or substitute decision-makers. The decision not to resuscitate may indicate that death is inevitable or that the patient has expressed a wish not to receive resuscitation or life-sustaining treatments. These decisions continue to be problematic and are frequently not documented in the patients’ case notes.

The quality of care of patients with ‘not for resuscitation’ documented can be inferior, including increased risk of death. In Australia, there is no consistent approach, protocol or policy about documenting or communicating resuscitation decisions. Advance care planning can improve end-of-life care for older people admitted to the hospital if their wishes are documented and followed, resulting in increased satisfaction with care and less likelihood of anxiety, depression and post-traumatic stress in the surviving relatives.

The aim of this exploratory study was to examine the frequency and clarity of the documentation about resuscitation in older patients’ case notes during their current and previous admissions within the past 5 years.

The clinical case notes of 99 patients admitted through emergency to the general medicine service at a South Australian major teaching hospital were audited over a 7-week period. General medicine is responsible for the care of complex, often older patients when a subspeciality unit, including geriatrics, is inappropriate.

The selection criteria included patients aged 70 years and over whose case notes had resuscitation documentation recorded within 48 h of admission. Ethics approval was given by the hospital’s Human Research Ethics Committee.

This case note review included identification of any advance care plans or a legal advance directive document that recorded the patients’ wishes and identified their substitute decision-makers, such as a medical power of attorney (MPA) or an enduring power of guardianship.

Demographic data were also collected, including age, gender, nationality and place of residence, and contextual data, such as time of admission and resuscitation documentation, and the apparent ability of the patient to participate in discussions.
The relevant documentation was deidentified and photocopied, and the terminology was transcribed and coded for qualitative analysis.12

The mean age (standard deviation) of the total population was 85 (6.5) years, and other characteristics of the patient or their admission are presented in Table 1.

Within 48 h of admission, 34 patients had resuscitation decisions documented in their case notes (Table 1). Fifty patients were assessed by our case note review as having the ability to discuss their resuscitation at the time of their admission. Of those, 16 (32%) had documentation. Two patients had documentation about their wishes in case notes of a previous admission, but not in the current admission, nor did their notes refer to their previous resuscitation wishes. Three patients were for full resuscitation, four patients were for no resuscitation and 27 were for MET calls but not for Code Blue.

For most patients with resuscitation documentation (26 of the 34), a discussion had occurred with the family or patient or both. For eight patients, it was not clearly stated whether any discussion about resuscitation had occurred within 48 h of admission, yet a decision was documented in the notes.

South Australian legal advance care directive documents were mentioned in two case notes, but in both cases the documents themselves were not available to the medical staff. A ‘good palliative care plan’ was available for two patients’ current admissions and in a previous admission for another patient. Only one of these was mentioned in the current documentation. A fourth patient had a residential care facility form called ‘Palliative Care Wishes’, which was dated 5 years prior to the current admission.

Acronyms referring to substitute decision-makers were documented in the current admission notes of two patients. Both stated that the family member was ‘EPOA and guardian’. In the nursing summary of a third patient, it was stated ‘daughters shared POA and POG’. A fourth patient had a detailed reference to the son having his mother’s ‘MPA’. The interpretation of these acronyms is unclear.13 There was no mention of any of these legal documents being sighted.

The documentation about resuscitation was difficult to read in at least seven cases. The acronyms and terms used and the order in which they were written varied from patient to patient and between admissions for the same patient. There was no standard list of potential treatment options (Table 2). The terminology was imprecise and lacked consistency.

In 28 (of 34) sets of case notes, the resuscitation decision was documented by the admitting officer in the admission entry; 15 were documented as part of the admission and 13 were added immediately afterwards as a postscript. The six remaining decisions were recorded within 48 h of the admission.

Resuscitation documentation was not entered in two thirds of older patients’ case notes within 48 h of their admission to an acute teaching hospital. The majority of documented decisions was for limited resuscitation. Twenty-eight of the 34 decisions were documented by

<table>
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<tr>
<th>Characteristic</th>
<th>Total population</th>
<th>Resuscitation documentation present</th>
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<tbody>
<tr>
<td>Number of subjects</td>
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<td>34</td>
</tr>
<tr>
<td>Males</td>
<td>47</td>
<td>20</td>
</tr>
<tr>
<td>Australia, New Zealand or United Kingdom born</td>
<td>60</td>
<td>22</td>
</tr>
<tr>
<td>Lives at home</td>
<td>78</td>
<td>22</td>
</tr>
<tr>
<td>Lives in low-level residential care facility</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Lives in high-level residential care facility</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Admitted between 0900 and 1700 h</td>
<td>33</td>
<td>10</td>
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</table>

### Table 2: Terminology used in patients’ case notes

<table>
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<th>Ward measures</th>
<th>Full measures</th>
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<td>HDU</td>
<td>Not for aggressive/invasive Tx</td>
<td>Ward measurement</td>
<td>Conservative ward Rx</td>
</tr>
<tr>
<td>HDV</td>
<td>Defib/Defibrillation</td>
<td>Medical ward care</td>
<td>Only for conservative ward Rx</td>
</tr>
<tr>
<td>HV</td>
<td></td>
<td>Ward medical measures</td>
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</tr>
<tr>
<td>NIV/Non-invasive ventilation</td>
<td>Ward management</td>
<td>Active ward management</td>
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<tr>
<td>I + V</td>
<td></td>
<td>Active ward management</td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td></td>
<td>Actives ward measure(s)</td>
<td></td>
</tr>
<tr>
<td>ICU + admission</td>
<td></td>
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</tbody>
</table>
the admitting doctor. The documentation was problematic because it lacked consistency in the use of acronyms and terms, and the text was difficult to read in at least seven cases. Less than a third of the 50 patients with the ability to discuss decisions had any documentation about resuscitation in their case notes.

Seven patients’ case notes stated that they were for limited or no resuscitation, yet there was no evidence of a discussion with the patient or their families. In 33 of the 34 documented resuscitation decisions, there was no indication of the information given to the patient or their family about resuscitation or whether the decisions were understood by them.

Conversations about death are difficult. They take time, training and effort and most importantly clinical leadership.1-4 We have shown that, even if such conversations occur, the standard of documentation is inadequate to guarantee good communication between clinicians and that good communication has occurred between clinicians and the patient. Increasingly, the role of the MET staff involves decisions and discussions about end-of-life care planning and resuscitation status.15 However, this seems not to be a clearly articulated policy and does not explain why most patients had no documentation in their case notes.

The different sequencing of words, terms and acronyms revealed no standard format for documenting resuscitation decisions. If there is no clearly documented plan for the care of the patient other than ‘do not resuscitate’, there is the potential for inadequate or poor-quality medical care.7,16 The meaning of the term ‘ward measures’ and its variations is unclear. Also, the terms ‘active ward measures’ and ‘ward measures only’ have a wide range of interpretation. This lack of precision in common terminology impairs good communication.

Although advance care planning and the use of legal advance care directive documents are now recognised in the literature,5-10 there was little evidence that these documents are being used or presented on hospital admission. None of the relevant legal documents expressing patients’ wishes was sighted. The language used in the case notes suggests that there is not a clear understanding of the differences between the enduring powers (substitute decision-makers) in the South Australian jurisdiction. The National Framework for Advance Care Directives, which has now been adopted by all Australian health ministers, recommends consistent terminology nationally to avoid confusion.13

Two thirds of patients had no current resuscitation documentation, yet two had some documentation from a previous admission. Knowing that a person had previously refused any form of resuscitation should prompt clinicians to revisit the conversation or at least note any previous decision in the current case notes.

Decisions about resuscitation raise ethical dilemmas in medicine, especially when associated with frail older patients. Hospitals are providing more extensive and progressively greater care for older people at the end of life, many of whom die with an illness for which palliative care is more appropriate than resuscitation.17 We need a better designed form and process, which includes discussions with patient and family, clear instructions about treatment if the patient arrests and care plans if resuscitation is not appropriate.16 There is an urgent need for clinical guidelines to assist clinicians introduce the conversation about the resuscitation decisions and to document these decisions, taking the patient’s wishes into account. Hayes5 has recently developed a model for ethical decision-making about CPR, which would include appropriate documentation to avoid inappropriate and unwanted resuscitation. Clear, contemporary and accurate documentation about the resuscitation of a patient is an important part of good medical practice. We call for an informed community debate on this topic. The community should to be involved; dying is a social issue, not just a medical one.

References
9 Sidhu NS, Dunkley ME, Egan MJ. ‘Not-for-resuscitation’ orders in Australian public hospitals: policies,


Use of infliximab and other biologics in Behçet disease

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Key words
Behçet disease, neuro-Behçet, infliximab.

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Behçet disease is a multisystem vasculitis characterised by recurrent oral ulceration in conjunction with other manifestations, which include genital ulceration and ocular and skin lesions. Neurological complications, when they occur, predominantly affect young men at their onset between the ages of 20 and 40 with significant long-term morbidity and mortality. Case literature mounts on the efficacy of tumour necrosis factor antagonists, notably infliximab, in the treatment of neuro-Behçet disease.

Our patient is now 37 years old. He is of Pakistani heritage, HLA-B51 positive and lives with 22 family members in New South Wales. At age 30, he noted oral and scrotal ulcerations, papulopustular lesions on his chest, nodules over both shins, an inflammatory polyarthropathy of the small joints of his hands and abdominal pain. These resolved spontaneously.

At age 32, he developed acute bilateral leg pain and urinary retention over 4 days. Neurological examination demonstrated flaccid paraparesis and a sensory level to T8. Leg weakness and paraesthesia rapidly progressed within 24 h of presentation. Empirically, he received intravenous methylprednisolone and broad spectrum antimicrobial therapy.

At 48 h, he reported new onset diplopia, upper limb tremor and right upper limb paraesthesia. We commenced intravenous immunoglobulin in addition to ongoing daily intravenous methylprednisolone. Magnetic resonance imaging (MRI) of the brain and spine revealed T2
hyperintensities in the pons, cervical and upper thoracic cord and conus medullaris (Fig. 1).

A clinical diagnosis of neuro-Behçet disease was formed based on the typical clinical and radiological findings and a lone raised cerebrospinal fluid protein of 2.4 g/L. Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-neuromyelitis optica antibodies and antiphospholipid antibodies were not detected. Serology for human immunodeficiency virus, human T-lymphotropic virus (HTLV) I/II, Mycoplasma pneumoniae and syphilis, and HSV and cytomegalovirus polymerase chain reaction in cerebrospinal fluid was negative. Serum electrophoresis/immunofixation electrophoresis, β2-microglobulin, lactate dehydrogenase, B12 and folate were within normal limits.

On day 4, he commenced plasmapheresis to five exchanges by day 9. Repeat MRI brain and spine showed significant improvement in all T2 hyperintensities (Fig. 1). His diplopia and upper limb symptoms completely resolved, but he remained wheelchair bound with an indwelling catheter in place.

Azathioprine, progressively increased to 150 mg, and infliximab were commenced in conjunction with 9 months of isoniazid prophylaxis. He received infliximab, which was well tolerated, at a dose of 5 mg/kg at weeks 0, 2 and 6, and then at maintenance 8-weekly intervals. This was increased to 6 weekly to improve his paraparesis. Prednisolone was weaned to cessation over a period of 12 months.

At 3 months, he could walk 100 m with a pick up frame, and at 12 months, independently, requiring a wheelchair only for long distances. All T2 hyperintensities on MRI brain resolved at 6 months, and on MRI spine, at 12 months. He intermittently self-catheterises, at reduced frequency, approximately twice a day.

He remains in clinical and radiological remission, to the time of publication, at 56 months.

The prevalence of Behçet disease in Western countries is estimated at 0.12–0.64/100 000 capita. Along the Silk Road, this figure rises to 10–100/100 000.4 Our patient clearly meets International Study Group criteria for Behçet disease (Fig. 2).1 Behçet disease is a clinical diagnosis based on the finding of recurrent oral ulcerations accompanied by two other criteria in the absence of alternative pathology. It is an important differential diagnosis to consider in clinical practice given the specific therapy that is available. The prevalence of neuro-Behçet disease is quoted at 1–59%.2 At highest risk of neurological and major organ involvement are young men.3,5 Infection, complications of treatment, uveomeningitic manifestations of systemic diseases, demyelination and neoplastic or...
paraneoplastic phenomena must be excluded prior to diagnosis.\(^2\) Additionally, neurological presentations should fall within a recognised pattern of parenchymal, or non-parenchymal disease.

Parenchymal disease is most common, typically affecting the brainstem alone or with another focus in the central nervous system (‘brainstem plus’), spinal cord or cerebral hemispheres.\(^6,7\) Our patient had ‘brainstem plus’ disease,\(^6\) with a unilateral enhancing T2 hyperintense lesion at the pons, a typical lesion in parenchymal disease and multilevel spinal cord lesions (Fig. 1).\(^8,9\) Other recognised sites of involvement on MRI brain are the mesodiencephalic junction, the diencephalon (thalamus and hypothalamus) and the basal ganglia.\(^3,8\)

The pathogenesis of Behçet disease is not known, but in vivo studies demonstrate increased expression of pro-inflammatory and Th1 type cytokines in active disease. Plasma levels of pro-inflammatory cytokines, principally tumour necrosis factor (TNF-\(\alpha\)), interleukin (IL)-1 and IL-8, are raised. Additionally, prominent tissue infiltration by TNF-\(\alpha\) positive cells occurs, as noted in the mucocutaneous ulcers of Behçet disease. Raised secretion of pro-inflammatory cytokines occurs following inflammatory stimulus in inactive disease.\(^10\) Infliximab, a monoclonal antibody directed against TNF-\(\alpha\), is consequently a good therapeutic candidate in the treatment of Behçet disease.

Case series demonstrate that infliximab is effective for treating acute ocular inflammation, and maintaining visual acuity in disease refractory to conventional immunosuppressive therapy.\(^11-13\) It was also effective for extracranial manifestations in these same patients.

While there are no equivalent studies evaluating the efficacy of infliximab in neuro-Behçet disease, numerous case reports demonstrate successful neurological outcomes. These reports suggest efficacy at a dose of 5 mg/kg administered at weeks 0, 2 and 6, and then at 8-weekly intervals, which can be increased to 6 weekly.\(^14\)

In Japan,\(^15\) five patients aged between 29 and 37 at onset of progressive neuro-Behçet disease refractory to methotrexate and prednisolone, were followed to 24 weeks. Infliximab at a dose of 5 mg/kg resolved or decreased the frequency of urinary incontinence in all three patients affected. It improved weakness in one
patient, and decreased the frequency of myoclonus in both patients affected. There was no effect on ataxia or dementia. Progression of chronic disease, defined in terms of brainstem atrophy, was arrested on MRI at 24 weeks. An Italian series described eight patients between the ages of 20 and 46 at onset, except for one patient aged 69.16 Clinical presentations again varied. Five cases of new onset neuro-Behçet disease and three cases of relapsed disease were described. Infliximab at a dose of 5 mg/kg was used for all patients, and apart from one case, administered at weeks 0, 2 and 6 and continued at 8-weekly maintenance intervals. Two patients, with onset of neurological symptoms at ages 41 and 69, sustained remission without maintenance infusions. All eight patients experienced improvement in all of their reported neurological manifestations, except for one patient who experienced initial improvement and no deterioration until the withdrawal of infliximab therapy at 60 months. Specifically, weakness improved in four patients and resolved in a fifth patient. Diplopia resolved at 60 months. Specifically, weakness improved in four patients and resolved in a fifth patient. Diplopia resolved at 60 months.

In Spain,17 relapsed neuro-Behçet disease was reported in a patient at age 52, characterised by headache and unilateral facial weakness. On MRI there were multiple T2 hyperintense lesions in both cerebral hemispheres. Infliximab was administered at a dose of 5 mg/kg at weeks 0, 2 and 6 and then at 8-weekly maintenance intervals with methotrexate. Clinical and radiological remission was reported to 12 months.

In Iran,18,19 case reports covered four patients between the ages of 30 and 43 at onset. In the unsuccessful cases, infliximab was administered at a lower dose of 3 mg/kg in two patients with relapsed neuro-Behçet disease. In the successful cases, infliximab was deployed at a dose of 5 mg/kg with prednisone and pulsed cyclophosphamide. Clinical and radiological improvement was sustained at 16 and 11 months in two patients with chronic progressive neuro-Behçet disease and new onset disease respectively. Improvements in weakness, urinary incontinence, paresthesia and altered sensorium were reported, but financial constraints curbed continuation of therapy.

We describe a young man, once wheelchair bound, who is in clinical and radiological remission from new onset neuro-Behçet disease on follow up at 56 months. At 37 years of age, he grapples daily with the physical and emotional burden of chronic neurological disease, but he is able to walk and is relatively independent.

Case literature supports the efficacy of infliximab at a dose of 5 mg/kg, in the treatment of new onset, relapsed and chronic progressive neuro-Behçet disease. Infliximab should be scheduled at weeks 0, 2 and 6, and then at 8-weekly maintenance intervals if required, which can be increased in frequency to 6 weekly if necessary. Consistent improvement or resolution of weakness, diplopia and behavioural changes have been reported, together with marked reduction or resolution of brain and spinal cord abnormalities on MRI.

Infliximab is the best studied biological therapy in the treatment of refractory Behçet disease. It will be interesting to see if future literature will show that newer biologicals, particularly anti-IL-1 and anti-IL-6 agents, will be efficacious in neuro-Behçet disease.20

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References


Practical aspects of telehealth: doctor–patient relationship and communication

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Key words telehealth, video consultation communication skills, telemedicine, doctor–patient relationship.

Abstract

The fourth in a series of articles about the practical aspects of telehealth, this paper provides advice and information for specialists to communicate effectively with patients during a telehealth video consultation.

Introduction

Doctor–patient communication during a medical consultation is an important part of any therapeutic relationship between a patient and their doctor. It is complex and affected by many factors including the personality and communication style of both the doctor and the patient, the physical environment and the level of education of the patient.1 Some studies on face-to-face consultations have reported a strong correlation between patient satisfaction and interview length and high levels of information received, whereas others found a correlation with affective behavior and in particular, the physical interaction.2

It is estimated that only 7% of emotional communication takes place verbally, whereas 22% is communicated by tone of voice and 55% by posture, gaze and eye contact.2 During a telehealth consultation, as the patient and the specialist are not in the same room, the dynamics observed in a video consultation can differ from a traditional face-to-face consultation. Therefore, it is understandable that there will be ongoing concerns regarding the doctor–patient relationship and rapport for the delivery of clinical services through a video consultation. Table 1 summarises selected studies, albeit small, that examined various aspects of telehealth consultations. As the issue of doctor–patient communication in technology is a complex and evolving topic, future in-depth qualitative studies are needed to explore perceptions of the patient and the doctor.

Many consultations are supported by rural-based doctors and nurses.6,8 This adds another dimension to the doctor–patient communication in that they can take the role of filling any perceived gaps in the communication between the specialist and patient. Video consultations also facilitate the presence of extended family members, which is an added advantage.

These studies show that patients can experience effective doctor–patient communication through technology-
based consultations and that the patients can establish closer relationships with specialists. Patients from a range of ethnic and cultural backgrounds have been able to build effective rapport with specialists through telehealth. It is the view of The Royal Australasian College of Physicians Telehealth Working Group that communication should be based on the needs of individual patients and their families rather than be prejudiced by ethnic backgrounds.

Practical tips for improving the quality of the doctor–patient communication for telehealth:

• Before starting the consultation, check that the audio and video components are both working and ensure that your image is in the middle of the screen and zoomed in so that you are clearly visible at the patient end.
• Introduce and greet parties at both specialist and patient ends of the consultation.
• Explain that whatever is covered in a traditional face-to-face consultation will be covered in the video consultation and that the level of service will be the same.
• If you have a webcam positioned at the top of your monitor/laptop, position the image of the patient end as close to the webcam as possible so that it appears you are making eye contact with the patient.
• Spend some time discussing family, home and other social matters to build rapport (as you would in face-to-face consultations).
• Maintain eye contact with the patient by effectively using the camera and zoom in and out to pick up any non-verbal cues.
• Effective transfer of information: the use of visual aids such as imaging studies and/or drawing on white boards can support verbal explanations.
• Summarise the consultation and check that the patient has understood the information.
• If the consultation involves the discussion of sensitive information, encourage family members and/or health professionals to participate in the video consultation at the patient end.
• Before completing the consultation, suggest opportunities for addressing future concerns by offering the contact details for local healthcare providers and other specialists.

Case 1: breaking bad news

A 56-year-old patient presents to a rural hospital with increasing dyspnoea because of extensive pulmonary metastasis secondary to colon cancer. She was too sick to transfer to a tertiary centre and was therefore seen urgently (within 24 h) by medical oncologists through telehealth. At the request of the treating team, many family members attended the video consultation. The consultation included discussions about the patient’s diagnosis, prognosis and future management and what the patient could expect from therapy. After ensuring that the family and patient had no further questions, the patient was able to be treated without leaving her home town and within 48 h of participating in the telehealth consultation. FOLFOX with bevacizumab was started, and after two cycles, the patient’s dyspnoea and quality of life improved.

Discussion

The patient’s initial diagnosis was determined by local internal physicians in close liaison with medical oncologists. On referral, it was obvious that the patient had an incurable and potentially rapidly fatal disease, hence the request for many family members to participate in the telehealth video consultation. By showing the scan on the screen, it was easy to explain to the patient and her family members why the cancer was incurable. The patient had the support of her family, a local nurse and doctors in the comfort of her home environment. This made it easier for all parties to accept and cope with the bad news. The patient had an excellent response to her first-line therapy and established a productive and close relationship with her local and remote healthcare teams.

Table 1 Selected literature for doctor-patient communication and building rapport for video consultations

<table>
<thead>
<tr>
<th>Authors</th>
<th>Setting</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmidt et al,1</td>
<td>Hospice patients</td>
<td>Varieties of facial expressions of emotions were observed. Expression of both positive and negative emotions were apparent.</td>
</tr>
<tr>
<td>Sabesan et al,4, Mooi et al,5, and Doolittle and Spaulling6</td>
<td>Medical oncology networks; questionnaire-based surveys of indigenous and non-indigenous patients.</td>
<td>More than 80% in agreement on a Likert scale for closeness of the relationship with specialists, ability to ask questions and satisfaction with overall care.</td>
</tr>
<tr>
<td>Mair and Whitten7</td>
<td>Systematic review of studies on patient satisfaction from many fields of medicine</td>
<td>Good levels of patient satisfaction were noted in most studies. Note: the studies were limited by small sample sizes.</td>
</tr>
</tbody>
</table>
Commentary
It is possible to conduct an initial consultation and discuss the patient’s prognosis through telehealth while establishing excellent rapport. The use of visual aids like CT images and the presence of local health professionals and family members make it easier for specialists to break bad news and for the patients to cope with the news.

Case 2: dealing with angry patients
A 60-year-old woman had been seeing a regional endocrinology team through telehealth. Her diabetes was out of control because of family circumstances. When her issues were explored during a video consultation she became defensive and angry. After giving her a few minutes to gather herself, she was able to continue with her consultation. A social worker was asked to join the telehealth video consultation to discuss solutions for the patient’s family issues.

Discussion
In this case, a technique that is used for face-to-face consultations was adopted to manage the situation for the telehealth video consultation. By being patient and giving her time to cool down, the video consultation was successfully completed. Unlike a face-to-face consultation where only the general practitioner or specialist sits with the patient and their family, nurses and other allied health professionals were able to provide comfort to the patient as well. In this case, the existing relationship between the patient and her healthcare team may have made the situation more manageable.

Commentary
This case demonstrates that, similar to face-to-face consultations, communication barriers can occur during telehealth consultations. Therefore, most communication skills that are applicable to face-to-face consultations can be applied to telehealth consultations as well.

Practical tips
1. Screens can be barriers to effective doctor–patient relationships, therefore connecting with the patient on the screen at human level rather than an image on the screen is important for an effective therapeutic relationship.
2. Most communication techniques used in face-to-face consultations are applicable to video consultations.
3. It is useful to have a mental framework/checklist to ensure every consultation is consistent and successful.

Conclusion
Effective doctor-patient communication is an essential component of a telehealth consultation. Sound communication and rapport between the doctor, patient and support staff can facilitate a satisfactory and positive experience for the patient and their family members. By applying some of the communication techniques used during face to face consultations, video consultations can provide a highly effective and convenient means of healthcare delivery for patients living in rural and remote areas, Indigenous communities and aged care facilities.

References
LETTERS TO THE EDITOR

Clinical-scientific notes

Late-onset type 1 diabetes in Pasifika migrants living in Auckland

Type 1 diabetes is usually thought of as a disorder of onset in childhood, adolescence or early adulthood. However, in recent years, aided by the availability of serological tests for islet cell autoimmunity, its presentation in older adults has become well recognised, particularly in people of European descent. In this age group, the disease is often of slow onset and commonly mistaken for type 2 diabetes.1

Type 1 diabetes is rare in Pasifika children living in the Pacific Islands, but does occur in the New Zealand-born offspring of migrants.2,3 In adults of Pasifika descent, type 2 diabetes is very common, primarily because of high levels of obesity, and it becomes even more prevalent after migration to westernised countries, such as Australia and New Zealand. To our knowledge, adult-onset type 1 diabetes in first-generation Pasifika migrants has not been recognised previously. We describe six such patients, all of whom were originally diagnosed with type 2 diabetes.

Details of the patients are given in the Table 1. One patient (no. 4) was diagnosed with diabetes before and one (no. 1) shortly after migration; the other four were diagnosed 9–33 years after migration. Only one (no. 6) had any known European ancestry. The interval between diagnosis of diabetes and starting insulin treatment was 0–3 years. Type 1 diabetes was confirmed by the finding of serum antibodies to glutamic acid decarboxylase and undetectable or low fasting C-peptide levels (an indicator of endogenous insulin production). The interval between diagnosis of diabetes and recognition that it was type 1 (rather than type 2) ranged from 2 to 19 years.

The clinical clues that led to the correct diagnosis were severe symptoms and rapid progression to needing insulin (two patients), labile blood sugars with hypoglycaemic episodes (three), diabetic ketoacidosis (one), the presence of other autoimmune disease (two) and a child in the family having type 1 diabetes (one). Insulin requirements for glycaemic control were relatively low (0.35–0.67 u/kg body weight). Factors that may have misled clinicians into continuing to believe that these patients had type 2 diabetes included the high mean body mass index (BMI) of 31 kg/m² (only one had a BMI < 25 kg/m²) and that most had features of the metabolic syndrome (dyslipidaemia and/or hypertension).

Type 1 diabetes is strongly associated with certain polymorphisms of the class II human leucocyte antigen (HLA) genes encoding DR and DQ, proteins that are involved in the regulation of immune responses. Genotyping of DQA1/DQB1 and DRB1 was performed using Luminex bead technology (One Lambda Inc., Los Angeles, CA, USA). Haplotypes were assigned based on known HLA-DQ–DR associations in Polynesians.4 In European subjects, five alleles have been particularly associated with susceptibility to late-onset type 1 diabetes,5 two of which were found in five of our patients: DRB1*0901-DQA1*0301-DQB1*0303 (three subjects) and DRB1*0403-DQA1*0301-DQB1*0302 (two subjects).

We conclude that type 1 diabetes can occur in adults of Pasifika descent, on a similar HLA background to that seen in European subjects. Consideration of all aspects of the phenotype aids accurate diagnosis, and this in turn should have a significant impact on treatment.

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Table 1 Clinical and biochemical findings in six Pasifika migrants to New Zealand with adult-onset type 1 diabetes

<table>
<thead>
<tr>
<th>Number</th>
<th>Gender – origin</th>
<th>Age [years] at Migration</th>
<th>Age [years] at Diagnosis</th>
<th>Start of insulin [year]</th>
<th>BMI (kg/m²)</th>
<th>Hypertension-dyslipidaemia</th>
<th>Anti-GAD (U/L)†</th>
<th>Fasting C-peptide (pmol/L)‡</th>
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<td>3</td>
<td>32</td>
<td>No-yes</td>
<td>&gt;250</td>
<td>253</td>
<td>0.61</td>
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</table>

†Normal <15 U/L. ‡Normal 370–1470 pmol/L. BMI, body mass index; GAD, antibodies to glutamic acid decarboxylase.
Baroreceptor failure related to bilateral carotid artery disease: an uncommon cause of labile hypertension

A 61-year-old woman was referred to a renal medicine clinic with labile hypertension resistant to combination therapy with five anti-hypertensive medications (candesartan, felodipine, metoprolol, bendroflumethiazide and spironolactone) at full dose for further management. She was asymptomatic and denied use of non-steroidal anti-inflammatory drugs, herbal or illicit drugs, or any symptoms suggestive of pheochromocytoma.

Her hypertension was first noted following a right hemiparetic transient Ischaemic attack about 9 years earlier. Her blood pressure (BP) was documented to be around 210/110 mmHg. Ultrasound carotid Doppler scans at that time revealed complete occlusion of the left internal carotid artery and 50–69% stenosis on the right side. By 2008, this stenosis had progressed to 75%, so she underwent right carotid endarterectomy (CEA) in that year. She also has a history of ischaemic heart disease and peripheral vascular disease and a strong history of smoking.

Her BP in the clinic was documented to be 215/106 mmHg with no significant discrepancy in four limbs; however, the patient reported her blood pressure can be as low as 80/40 mmHg on 4–5 days every 2 weeks and feels dizzy and fatigued at that time.

She had normal renal functions, thyroid function tests, plasma renin, aldosterone and catecholamine levels were within normal ranges. Her 24 h ambulatory monitoring revealed labile blood pressure with a daytime average of 154/82 mmHg and nocturnal average of 130/70 mmHg, indicating a likely degree of ‘white coat’ effect; however, her blood pressure records were fluctuating between a systolic blood pressure of 220 and 70 mmHg.

Computerised renal arteriography showed marked atherosclerotic disease of the abdominal aorta and renal arteries but no significant renal artery stenosis.

A tilt table test confirmed autonomic dysfunction by demonstrating a significant fall in systolic and diastolic blood pressure without compensatory increase in her heart rate.

Carotid baroreflex failure was considered as a factor contributing to her labile hypertension related to CEA with extensive contralateral carotid atherosclerosis. This case highlights the rare case of bilateral carotid artery disease causing baroreflex failure contributing to labile hypertension.

The arterial baroreflex acts primarily to calm unwarranted fluctuations in blood pressure on a minute-by-minute basis. Mechanoreceptors, sensitive to the stretch of vessel walls, are located within the tunica adventitia of each carotid sinus, the aortic arch and the pulmonary vasculature. The carotid sinus baroreceptors lie at the origin of the internal carotid arteries, from where afferent nerve fibres join the glossopharyngeal nerve to synapse in the nucleus tractus solitarius (NTS) of the dorsal medulla. The NTS then indirectly mediates autonomic outflow to the cardiovascular system through centres in the ventrolateral medulla.1

Ketch et al. describe ‘four faces of baroreflex failure’ – hypertensive crisis, volatile hypertension, orthostatic tachycardia and malignant vagotonia. Volatile hypertension is the most frequently encountered, and the most attuned to this case. It may develop insidiously and is characterised by symptomatic surges of blood pressure, which tend to moderate over time giving way to hypertensive episodes.2 It is common for patients with baroreflex failure to have low resting blood pressure.3 This pattern naturally presents a therapeutic challenge to clinicians, mandating frequent follow up and careful titration of antihypertensives.
Clinically significant damage to the afferent limb of the baroreflex arc seems to be uncommon and largely iatrogenic in origin. Offending procedures cited in case reports include unilateral and bilateral CEA,4,5 carotid body tumour resection6 and radiotherapy for throat cancer.1,7,8 Non-iatrogenic causes are trauma, tumour growth and afferent sensory neuropathy.2 In addition, brainstem stroke may impair function of the NTS or autonomic centres.

CEA is a common surgical procedure, performed on the evidence that it improves cerebrovascular prognosis in patients with significant (>70%) internal carotid artery stenosis.9 The association of CEA with perioperative haemodynamic instability is well recognised and attributed to acutely altered baroreflex function.7 The full-blown clinical picture of baroreflex failure (after unilateral CEA) appears to be rare but points out that compensation from contralateral carotid and aortic baroreceptors is likely to be a major protective factor, which may be compromised by the presence of atheroma10 and the effects are likely to be most marked when atheroma is circumferential around the carotid sinus.11,12 We hypothesise that this was likely in our case of an arteriopath with known total occlusion of the contralateral internal carotid artery and extensive atherosclerosis of the aorta.

Labile hypertension can be confirmed by 24 h ambulatory blood pressure monitoring. Impairment of the baroreflex may also be revealed by absent bradycardia in response to a pressor (phenylephrine) or absent tachycardia in response to a depressor (nitroprusside). Additional reflex tests are responses to valsalva manoeuvre, cold pressor, tilt table and handgrip tests.1,3,14

The goals of treatment are first to prevent episodes of extreme hypertension, and second to eliminate symptomatic hypotension and bradycardia and avoidance of vasodilators like calcium channel blockers. Clonidine is the drug of choice reducing both the frequency and severity of hypertensive episodes by attenuating sympathetic outflow.14,15 Unfortunately, our patient could not tolerate clonidine, feeling dizzy and fatigued. High-dose benzodiazepines, as well as behavioural therapy and relaxation techniques, may also be effective in preventing sympathetic surges.2,3,14

References


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Purple toes syndrome following stroke thrombolysis and warfarin therapy

An 85-year-old woman with a 20-year history of hypertension and hypercholesterolaemia who was in atrial fibrillation presented with an acute right middle cerebral artery infarct and was thrombolysed with recombinant tissue plasminogen activator in the third hour after onset. She was started on warfarin with enoxeparin bridging 4 days later and went home after 3 weeks on a therapeutic international normalised ratio (INR) of 2.2. Three weeks later, she developed fever and myalgia in the lower limbs. A day later, a reddish macular rash appeared on the shins and calves along with painful purple discolouration of the toes and the soles of the feet bilaterally, which progressed over 48 h. The distal pulses were well felt, and the capillary refill in the toes was normal. The discolouration had severe burning pain, was tender and cool on palpation, blanched with pressure and reappeared immediately afterwards (Fig. 1). There were no similar lesions in any other parts of the body. Blood investigations showed an elevated INR of 4.2, haemoglobin 116 g/L, white cell count $8.4 \times 10^9/L$, elevated eosinophil count of $0.9 \times 10^9/L$, platelet count $380 \times 10^9/L$, C-reactive protein 64 mg/L. There was new onset renal impairment with creatinine of 126 mmol/L and urea 14 mmol/L. Protein C, protein S, antithrombin III, antinuclear antibody, antineutrophil cytoplasmic antibody, antiphospholipid and lupus anticoagulant antibody levels were normal. Vascular Doppler of the lower limbs showed normal arterial flow and no evidence of venous thrombosis. The clinical presentation was consistent with purple toes syndrome and cholesterol embolisation syndrome secondary to oral anticoagulation. Warfarin was stopped, and enoxeparin 40 mg sub cutaneous once daily was started. The INR lowered to 1.3 after 36 h. Over the next few days, the skin of the left big toe developed pregangrenous changes. She died a week later from renal failure and sepsis. A skin biopsy could not be performed.

Purple toes syndrome or trash foot is reported infrequently after catheter angiography, aortic surgery, thrombolytic therapy and anticoagulant therapy. It results from cholesterol embolisation caused by distal showering of cholesterol crystals from atheromatous aortic plaques into the circulation of the distal lower limbs, causing occlusion and inflammation of dermal arterioles, ischaemic infarction of the epidermis, desaturation of blood and cyanosis in the toes and feet. It is a very rare complication after initiation of warfarin therapy and develops acutely 3–8 weeks later. Warfarin is thought to interfere with the protective thrombus on the surface of ulcerated aortic atheromatous plaques causing plaque haemorrhage, thus exposing the cholesterol core to distal embolisation. The risk of cholesterol embolisation syndrome is thought to be relatively low on INR maintained between 2 and 3. The high INR of 4.2 at presentation and thrombolysis with tissue plasminogen activator that preceded warfarin treatment are probable factors that precipitated aortic plaque destabilisation and subsequent cholesterol embolisation, purple toes syndrome and renal failure in our patient. Warfarin-induced skin necrosis is a differential diagnosis, which is distinguished by its onset in the first week of warfarin administration and its distribution in the breast, abdomen and hip regions.

Purple toes syndrome may be the presenting symptom of a more widespread cholesterol embolisation syndrome, which has the potential to cause multi-organ involvement of brain, eyes, gastrointestinal tract and kidneys, in addition to the skin and muscles of the lower limb extremities. It mandates cessation of oral anticoagulation in the acute stage to mitigate the risk of multi-organ dysfunction, including renal failure from continued cholesterol embolisation. This rare condition needs to be kept in mind when encountering new cutaneous manifestations.

Figure 1  Reddish macular rash on the shins, purple discoloration of the toes and soles of the feet with pregangrenous change of the left big toe.
in the lower limbs after recent initiation of warfarin and high INR especially if preceded by thrombolysis.

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References


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Whose responsibility is it to assess cardiovascular risk in patients with rheumatoid arthritis?

Cardiovascular disease (CVD) is a significant cause of morbidity and mortality in rheumatoid arthritis (RA), accounting for 40–50% of all deaths in this disease.¹ ² There is an increasing body of evidence suggesting that this risk can be substantially reduced through tight control of disease activity³ ⁴ and optimisation of ‘traditional’ CVD risk factors. In 2010, the European League Against Rheumatism (EULAR) released evidence-based recommendations to assist clinicians in managing CVD risk in patients with RA.⁵ These recommendations may be summarised as tight control of RA disease activity while limiting corticosteroid use, annual assessment of CVD risk factors such as lipids and blood glucose, smoking cessation, use of statins, angiotensin-converting enzyme inhibitors and angiotensin type II receptor blockers where indicated, and judicious use of non-steroidal anti-inflammatory drugs.

We reviewed the records of 75 consecutive patients with RA (fulfilling the American College of Rheumatology classification criteria⁶), attending the rheumatology outpatient clinic at St Vincent’s Hospital Melbourne between June 2010 and January 2012, in order to determine the adequacy of CVD risk assessment and documentation as per the EULAR guidelines. We were surprised to find that CVD risk assessment and management were suboptimal. Blood pressure (BP) measurements were only documented in 15% of all patients, and of the patients with known hypertension, only 12% had BP measurements recorded. Only 23% of patients completed a fasting blood glucose test in the previous year, whereas only 17% of patients receiving statin therapy (and therefore at higher risk of diabetes) had a documented blood glucose measurement within the past year.

Lipid levels were recorded in the past year for only 23% of all patients, whereas only 17% of patients with ischaemic heart disease had lipid measurements recorded. Although 6% of patients were current smokers, the smoking status of 81% of patients remained unrecorded. Management of CVD risk factors was also out of line with EULAR recommendations, with 23% of hypertensive patients not receiving antihypertensive treatment. Despite 51% of patients having multiple risk factors for CVD, only 36% of patients were receiving statin therapy at most recent review.

So, is the inadequate assessment and management of CVD risk in RA due to a lack of time and resources, or can it be attributed to a lack of knowledge of the breadth, or even existence, of the EULAR recommendations within the local medical community? Is the management of CVD risk in RA the responsibility of the treating
rheumatologist or the general practitioner? Given the complexity of management of RA and the need to address ancillary issues such as CVD risk, clinical nurse educators may play a key role in a ‘shared care’ model, ensuring that this important aspect of RA management receives the attention it deserves.

Acknowledgement

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References


Patient perspective: what would Donabedian say?

A Donabedian perspective is pertinent to the review article by Chalwin and Flabouris. Avedis Donabedian was an international leader in public health who provided key contributions to the fields of health services and quality of healthcare. He believed that two elements were instrumental to the performance of practitioners: (i) technical skill and (ii) interpersonal skill. Donabedian lamented that interpersonal skill was ‘so important (but) so often ignored . . . (as) the criteria and standards that permit precise measurement of the attributes of the interpersonal process are not well developed’. No doubt Donabedian would have been delighted that there are now validated assessment tools for non-technical or ‘interpersonal’ skills in medical emergency teams (MET) and rapid response systems (RRS), as was outlined by Chalwin and Flabouris.

But what of patient communication? Many of the non-technical skills (NTS) assessment tools appraise communication between team members in a MET/RRS. However, a MET call is a frightening, bewildering and often perplexing event for a patient. Patients may feel they are being ‘spoken over’ and events are not properly explained. Patient-centred care is a component of quality, and the physician–patient interaction is a vitally important aspect to the delivery of care. It is a non-technical or ‘interpersonal’ skill. As such, how can we best assess the physician–patient interaction in an emergency setting?

Donabedian outlined the importance of structure, process and outcome to evaluate the quality of healthcare, known as the Donabedian Quality-of-Care Framework.
in which care occurs, process indicates what is actually done in receiving care and outcome reflects the effects of care on the health status of patients and populations. To assess communication with the patient, one could observe the physician–patient interaction as a process, in the same manner that the validated NTS assessment tools evaluate emergency team interactions. However, an even more powerful tool might be the outcome measure of patient satisfaction. Patient satisfaction in emergency settings has been explored in several studies. One review found that empathy and information dispensation were key elements of patient satisfaction in an emergency department. Patient satisfaction assessments can provide insight into perceptions of NTS in emergencies.

What would Donabedian say? As a public health pillar ahead of his time, I cannot profess to know. I can only speculate that Donabedian would congratulate those who are developing tools to assess interpersonal skills, a key component of quality. However, he may remind us of the importance of incorporating the ‘patient experience’ in an assessment of NTS.

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References
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