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Soliris® (eculizumab, rmc) is now PBS (Section 100) listed for the treatment of aHUS*

IN PATIENTS WITH aHUS, SOLIRIS:

• Inhibits complemented-mediated TMA²
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Early intervention with Soliris in aHUS is vital in maximising clinical benefit³

Soliris in aHUS · Targets the cause · Protects vital organs · Transforms lives²

*For details of the PBS Section 100 eligibility criteria for aHUS, contact Medical Information at Alexion. Telephone 02 9091 0500 or email alexion.australia@alxn.com

aHUS = atypical Haemolytic Uraemic Syndrome. TMA = Thrombomicroangiopathy.
**SOLIRIS® (eculizumab, rmc) Minimum Product Information.**

**INDICATION:** Treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) to reduce haemolysis and patients with atypical haemolytic uraemic syndrome (aHUS).

**CONTRAINDICATIONS:** Hypersensitivity to eculizumab, murine proteins or excipients.* Do not initiate in PNH patients with unresolved Neisseria meningitidis infection or who are not currently vaccinated against *Neisseria meningitidis*. Do not initiate in aHUS patients with unresolved *Neisseria meningitidis* infection, who are not currently vaccinated against *Neisseria meningitidis* or who do not receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. **PRECAUTIONS:** Meningococcal Infection – see Boxed Warning – Provide patients with a patient information brochure and safety card and instruct to seek medical care if they develop fever > 39°C, headache accompanied by fever and/or stiff neck or sensitivity to light. **Immunisation** – In addition to meningococcal vaccination (see Boxed Warning), follow national immunisation guidelines; patients below the age of 18 years must be vaccinated against *Haemophilus influenzae* and pneumococcal infections and strictly adhere to vaccination recommendations for age group. Other Systemic Infections – Patients may have increased susceptibility to infections, especially with encapsulated bacteria.* Administer with caution to patients with active systemic infections. Provide patients with information from the CMI to increase their awareness of potential serious infections and the signs and symptoms of them. Discontinuation – Closely monitor any PNH patient who discontinues treatment for at least 8 weeks to detect serious intravascular haemolysis and other reactions. Closely monitor any aHUS patient who discontinues treatment for at least 12 weeks to detect serious thrombotic microangiopathy complications. Anticoagulation Therapy – SOLIRIS® should not alter anticoagulant management. PNH Laboratory Monitoring – Measure serum LDH levels, monitor for signs and symptoms of intravascular haemolysis. Patients may require dose adjustment within the recommended 14 ± 2 day dosing schedule during the maintenance phase (up to every 12 days). Infusion Reactions – Administration may result in infusion reactions or immunogenicity that could cause allergic or hypersensitivity reactions (including anaphylaxis). Interrupt administration in all patients experiencing severe infusion reactions and provide appropriate medical therapy. Use in Pregnancy-Category B2 – Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. Use in Lactation – Discontinue breastfeeding during during treatment and up to 5 months after treatment. Paediatric Use – Safety and effectiveness in PNH paediatric patients below the age of 18 have not been established. Use in the Elderly – In PNH studies the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients. In aHUS studies only one patient was over the age of 65.

**SOLIRIS® contains 5.00 mmol sodium per one vial which should be taken into account for patients on a controlled sodium diet:** ADVERSE EFFECTS: Common: Headache, dizziness, nausea, pyrexia, infection, leucopenia. Most serious adverse reaction in clinical trials was meningococcal infection. In aHUS patients aged < 12 years of age: diarrhoea, vomiting, pyrexia, upper respiratory tract infection and headache. **DOSAGE AND ADMINISTRATION:** Patients must be administered a meningococcal vaccine at least 2 weeks prior to initiation of therapy or receive prophylactic antibiotic treatment for at least 2 weeks after vaccination. Patients must be revaccinated according to current medical guidelines for vaccine use. **Dosage in PNH** – 600 mg every 7 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 days later, then 900 mg every 14 days thereafter. Administer at the recommended regimen time points or within two of these time points. **Dosage in aHUS** – Adults (≥ 18 years of age): 900 mg every 7 days for the first 4 weeks, followed by 1200 mg for the fifth dose 7 days later, then 1200 mg every 14 days thereafter. Administer at the recommended time points or within two of these time points. See full PI for dosing in patients < 18 years of age and for supplemental dosing in the setting of concomitant plasmapheresis, plasma exchange or fresh frozen plasma infusion. **Administration:** Dilute to a final concentration of 5 mg/mL according to recommendations in the full PI. Do not administer as an intravenous push or bolus injection. Administer by intravenous infusion over 25 to 45 minutes via gravity feed, a syringe-type pump, or infusion pump. If an adverse reaction occurs, the infusion may be slowed or stopped at the discretion of the physician. Total infusion time should not exceed two hours in adults and adolescents and four hours in children less than 12 years of age. Monitor the patient for at least one hour following completion of the infusion for signs of an infusion reaction. To reduce the microbiological hazard, use as soon as practicable after preparation. If necessary, hold at 2°C to 8°C for not more than 24 hours. **Date of most recent amendment:** 25 February 2014. *Please note changes to Product Information.*

Please refer to the Australian Product Information for Soliris (eculizumab, rmc) before prescribing Soliris, including Boxed WARNING regarding serious meningococcal infection. Please contact Alexion Pharmaceuticals Australasia Pty Ltd on 1800 788 189 to request the Full Product Information.

**PBS Information:** This product is listed on the PBS as a Section 100 item for the treatment of aHUS. Refer to PBS Schedule for full authority information. Soliris (eculizumab) is funded on the Life Saving Drug Program for the treatment of PNH. Application and consent forms for Soliris treatment are available from the LSDP website: http://www.health.gov.au/lsdp#Eculizumab


Internal Medicine Journal

The Official Journal of the Adult Medicine Division of The Royal Australasian College of Physicians (RACP)

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This is my 10th consecutive annual summary editorial, and I am very proud of the achievements of the editorial board and the management team for the entire decade. The *Internal Medicine Journal* continues to improve in scope, quality and reach, and our feedback is increasingly positive. The past year has been fantastic in terms of quality and publication timeliness. I hope you agree.

After a stable board during 2013, I am sad to announce the departure of three valued editors: Professor David Murdoch (Infectious Diseases), Dr John Vinen (Emergency Medicine) and Professor Anne Duggan (Gastroenterology). These long-serving editors have our eternal thanks for the excellent jobs they did in their individual portfolios and as members of a great team over a long period. They were replaced by Professors David Gordon, Paul Middleton and David Russell in their respective portfolios. Professor Mark Mclean announced his intention to resign at the end of the year from the Endocrinology portfolio. We will certainly miss Mark’s major contribution to the Journal as well and are thankful to have Associate Professor Morton Burt as the existing second Endocrinology editor, available to assist during the transition period while a new editor is sought. I welcome our new board members who have already contributed greatly to the workings of the Journal. This includes Dr David Blacker, who succeeded Peter Gates as Neurology editor. As an aside, the Cardiology subspecialty was divided into Cardiology (General) (Dr Paul Bridgman) and Cardiology (Arrhythmias) (Associate Professor Andrew McGavigan) with Andrew McGavigan’s previous title of ‘Deputy’ editor replaced by full editorship reflecting subspecialisation journal workload.

Our Thomson Reuters impact factor for 2013 showed a small decrease to 1.699, but this was not unexpected as a result of the publication policy of the past 2 years to increase significantly the number of papers published. This strategy successfully eradicated prolonged publication delays, but the increased numbers of published papers over 2 years did increase the denominator used to calculate the impact factor. In absolute terms, there were over 600 citations to papers in our journal in 2013 compared with just over 400 in 2012. The top cited paper in 2013 was the paper by Lai *et al.* in 2012 on variability in vitamin D assays,1 with the paper by Cheng *et al.* describing diabetes as a risk factor for dementia2 a close second. The number of full-text downloads of articles increased by 7% in 2013, suggesting that the content is increasingly valuable to many readers around the globe. The most downloaded paper in 2013 was that of Gates on brain stem anatomy for the non-neurologist,3 an oldie but clearly a goodie. I am proud that a former member of our editorial board takes that honour. The quality of papers we published in 2014 provides a positive framework for the next two years of impact factor calculations.

2013 was the 75th Anniversary of the Royal Australasian College of Physicians: many would have noticed the special logo that adorned the cover of the Journal and hopefully also during 2014 a series of specially badged commemorative papers by three esteemed former editors-in-chief, Michael O’Rourke,4 Edward Byrne5 and Graham Macdonald,6 and I was proud to have been able to write the introductory piece to that series.7 I would recommend that all readers have a look at these as they provide a fascinating insight into the eras represented by these people and beyond and in particular the place of this journal in those eras.

Two commemorative papers were published in the September 2014 issue of the Journal for the 20th Anniversary of the formation of the Australasian Faculty of Occupational and Environmental Medicine, offering Australian and New Zealand perspectives.

I suspect that no one can remember a time when Virginia Savickis was not the editorial manager of the journal. She has continued to do what she does best at a globally competitive standard, ensuring the quality production of our publication and smoothing the work for the editors. Lorelie Willoughby had functioned as editorial office administrator assisting Virginia for many years, and she has left the Journal after years of excellent service. Her role has been taken over by Louise Young-Wilson, who was an existing employee within Education Services in the College. We look forward to a long and fruitful relationship with Louise as well.

If you have not done so already, please subscribe to receive the table of contents to be provided to you automatically for alerts 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 through the publications link at http://www.racp.edu.au. I would recommend you explore this if you have not...
done so already. All published papers of the Internal Medicine Journal and its predecessors are accessible here as well the Virtual Issues series that we began in 2010. In 2014, we published virtual issues on haemostasis/thrombosis, rheumatology, neurology and geriatric medicine, and we plan to continue a reinvigorated series over the coming year.

The issue of the reviewing process for manuscripts submitted to medical and scientific journals remains controversial. At Internal Medicine Journal we firmly believe in the peer-review process. No one is better able to judge the value of a submitted paper than independent experts in the field and, despite some authors not appreciating some comments from reviewers, on balance all should be aware that the majority of papers are improved by the review process. It may mean that that submission needs to go elsewhere, but it should always be better than the version that had previously been rejected if reviewers’ comments are heeded. So, as I usually do, I thank our overworked and time-poor manuscript reviewers for the wonderful work they do for us and the authors whose submissions they review and always improve. If I could, I would triple the amount they are paid for this work (that would still be nothing!). I implore you to read their names listed after this article and thank them in some way. This would be a very different journal without each one of them.

I anticipate great things for our journal over the coming years. Please be an active part of it. Submit your best (or near best work) here and we will all be rewarded.

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J. Szer
Editor-in-Chief,
Internal Medicine Journal

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Colorectal cancer screening
B. A. Leggett1,2,3 and D. G. Hewett3,4

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Key words
colorectal cancer, bowel cancer, screening, colonoscopy, faecal occult blood test.

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Abstract
Colorectal cancer is one of the most common malignancies in Australia, and screening to detect it at an earlier stage is cost-effective. Furthermore, detection and removal of precursor polyps can reduce incidence. Currently, there are limited data to determine the screening rate in Australia, but it is certainly lower than the 80% screening rate considered desirable. Whether colonoscopy is used as the screening test or to follow up positive results of an initial non-invasive test, it plays a fundamental role. Despite high sensitivity and specificity, it is expensive and invasive with measurable risk and is not acceptable as an initial test to many participants. It does not provide complete protection, and interval cancers between planned colonoscopies are associated with proximal location, origin in sessile serrated adenomas and operator-dependent factors. An essential component of colorectal screening is the measurement of colonoscopy quality indicators, such as caecal intubation and adenoma detection rates, which are known to be associated with the rate of interval cancer. The non-invasive screening test currently recommended in Australia is biennial testing for faecal occult blood between the ages of 50 and 75 using a faecal immunochemical test, with positives evaluated by colonoscopy. This is provided through the National Bowel Cancer Screening Programme, currently for those at the ages of 50, 55, 60 and 65 years, with full implementation of biennial screening by 2020. To improve screening in Australia, the most fruitful approach may be to acknowledge that there is a choice of screening tests and to focus on the goal of improving overall participation rate and being able to measure this.

Introduction
Colorectal cancer (CRC) is one of the most common internal malignancies in Australia today, accounting for 12.6% of all new cancers and causing 3982 deaths in 2010. The risk of an Australian developing bowel cancer before the age of 85 is 1 in 12. The Australian age-standardised incidence rate is estimated to be the third highest in the world, after Slovakia and New Zealand. Over the past 30 years, the age-standardised incidence rates have remained relatively stable, with the increased numbers of new cases largely due to population growth and ageing. The average age of diagnosis is 69.3 years and the disease is uncommon under the age of 50.

Due to better treatment and perhaps earlier detection, 5-year survival rates have improved from 48.0% in 1982-1987 to 66.2% in 2006-2010. Survival is much better in earlier stage disease, and treatment of advanced disease with adjuvant or palliative chemotherapy in addition to surgery is costly. Thus, screening to detect CRC at an earlier stage is clearly worthwhile. However, the good news about CRC is that, unlike most other solid tumours, we understand a great deal about its premalignant phase and have the opportunity to interrupt this pathway before cancer develops.

CRC arises in pre-existing benign polyps, which occur due to genetic alterations in normal colonocytes (Fig. 1). Progressive accumulation of further genetic abnormalities over the years leads some polyps to enlarge, become severely dysplastic and develop into invasive malignancy. Approximately 80% of cancers arise in conventional adenomatous polyps with a genetic defect in the WNT pathway, and 20% arise from the recently recognised sessile serrated adenoma with a genetic defect in the MAPK pathway and heavy DNA methylation. Removal of colorectal polyps during colonoscopy is very effective in preventing CRC mortality, as shown by two recent studies with very long follow-up periods.
Guidelines from many parts of the world, including the USA, Europe and Australia, all endorse screening for CRC beginning at the age of 50.7–9 Patients with symptoms should undergo diagnostic testing (not screening), and those with a strong family history or long-standing inflammatory bowel disease may need to undergo screening at a younger age. The age at which to stop screening is not precisely defined, but by the age of 85 the risk of screening likely outweighs the benefit, and between the ages of 75 and 85 the decision needs to be individualised depending on health comorbidities.10 Possible screening strategies include colonoscopy every 10 years or initial non-invasive testing, most commonly annual or biennial faecal occult blood testing, with positives evaluated by colonoscopy. Faecal occult blood testing is an endorsed recommendation in Australia, Europe and USA, while American guidelines also endorse screening by colonoscopy every 10 years.7 There is very strong evidence that these strategies decrease CRC mortality and also decrease the incidence of CRC due to removal of premalignant polyps5,6,11 In fact, US screening guidelines distinguish between two categories of screening tests: (i) faecal tests, which primarily identify cancer; and (ii) structural tests, which both detect cancer and prevent its development through identification and removal of precursor lesions (Fig. 2).

**CRC screening in Australia**

Australian guidelines9 recommend biennial faecal occult blood tests for people categorised at or slightly above-average risk. Since 2006, the Australian Government has implemented a programmatic approach to screening, and has posted tests to individuals turning 55 or 65 and more recently those turning 50 or 60 as part of the National Bowel Cancer Screening Programme (NBCSP). Continued expansion of the NBCSP will achieve biennial screening for Australians at the ages of 50–74 years by 2020. There has been an approximately 40% participation rate in this programme, but to date it has only

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**Figure 1** Colorectal cancer precursors seen at colonoscopy: (A) conventional tubular/tubulovillous adenomas; (B) sessile serrated adenomas.
covered a very small fraction of those for whom screening is appropriate. Data suggest that if screening is performed outside this programme, it is most commonly by colonoscopy.12

There has been a marked growth in the provision of colonoscopy in Australia, 13 and even if the procedure is performed for an indication other than screening, polyps and cancers should be detected. A population-based survey of asymptomatic Australians at the ages of 56–88 years showed that 20% had undergone faecal occult blood testing in the preceding 2 years and 16% had undergone colonoscopy in the preceding 5 years.14 Thus, the proportion of people who could be considered ‘up to date’ with screening is higher than that recorded by participation in the organised programme (currently targeting those at the ages of 50, 55, 60 and 65), and better data are required to understand where the ‘gaps’ in screening exist and how to best target screening. Certainly, Australia has not achieved the 80% screening rate that the Centers for Disease Control and Prevention hope to achieve in the USA by 2014.15 Currently, the screening rate in the USA is approximately 65%.15

Whether colonoscopy is used as the screening test, or is used to evaluate further patients with positive results from an initial non-invasive screening test, it plays a fundamental role in the diagnosis of both polyps and cancer, and as a therapeutic tool for preinvasive disease. Therefore, we are first going to discuss quality issues related to the risks and benefits of colonoscopy and appropriate intervals for colonoscopic surveillance. We will also discuss constraints on its availability and its acceptability to screening participants in the Australian context. Following this, we will discuss the role of non-invasive screening tests such faecal occult blood tests and assessment of genetic risk in ‘triaging’ towards colonoscopy. Finally, we will discuss the possible integration of these various strategies to maximise prevention of CRC mortality in Australia.

Colonscopy

Colonoscopy is the final common step in all CRC screening pathways, irrespective of the choice of test. It offers direct visual inspection of the entire colon, immediate therapeutic intervention for removal of precancerous lesions, single test evaluation and therapy, and long-lasting cancer protection without the need for interval screening. However, colonoscopy is invasive, requiring time off work and awareness of its risks, including perforation and, in Australia where patients are typically sedated, of sedation complications.

Effectiveness of colonoscopy

Evidence for the effectiveness of colonoscopy in detecting and preventing CRC derives from indirect and observational data, rather than randomised trials. Case–control and cohort studies have demonstrated reductions in CRC incidence after initial screening colonoscopy of up to 70%,5,6,16,17 and up to 68% reductions in CRC mortality after over 15 years of follow up.5,16 Furthermore, in the USA, where colonoscopy has been a dominant screening modality for over a decade, rates of CRC have fallen.18 Three large randomised controlled trials evaluating the effectiveness of colonoscopy for CRC screening are ongoing, and not due to report for at least 10 years. US19 and Spanish20 trials are comparing one-time screening colonoscopy with faecal immunochemical testing (annual or biennial), and a further Nordic-European trial is comparing screening colonoscopy with no screening.21 However, colonoscopy is not perfect, and high levels of protection against CRC after colonoscopy are not assured. Despite community and general practitioner perceptions of a ‘guarantee’ against CRC from colonoscopy, approximately 6% of CRC occur within 5 years of a colonoscopy.22 The occurrence of these early, so-called interval cancers after clearing colonoscopy counteracts the protective effect of polypectomy on long-term CRC incidence.23 These interval lesions contribute to significant variation in published levels of CRC protection after colonoscopy.

Furthermore, the protective effect of colonoscopy does not appear to be uniform through the colon. Cohort and case–control studies from North America and Europe have shown that colonoscopy is less effective at preventing cancers in the proximal colon, compared with
Colonoscopy achieves substantial reductions in risk of distal CRC mortality (of up to 84%), but significantly lower risk reductions in the proximal colon, with some studies showing no benefit at all.24

Why does colonoscopy fail?

Interval cancers, or post-colonoscopy CRC, are defined as cancers occurring more than 6 months after colonoscopy but before the next scheduled CRC screening. Although uncommon, rates of interval cancer are an important outcome measure of colonoscopy against which other process measures of colonoscopy quality are validated. The majority of interval cancers are thought due to lesions missed at baseline colonoscopy, or polyps that were incompletely removed.22,28,29 Interval cancers represent a failure of colonoscopy and provide important information about its limitations in efficacy and effectiveness.23,30

Interval cancers, compared with non-interval cancers, are more likely to occur in the proximal colon (Fig. 3). They are associated with higher rates of baseline adenomas and a family history of CRC.22 Interval cancers are also more likely to have characteristic molecular features, including the CpG island methylator phenotype (CIMP) and microsatellite instability indicating a loss of function of DNA mismatch repair genes.6,31,32 These characteristics suggest the presence of altered tumour biology in interval cancers, and specifically implicate the serrated pathway of colorectal neoplasia and its precursor lesion, the sessile serrated adenoma.4,13

Sessile serrated adenomas are difficult to see at colonoscopy.3 They are typically very flat, pale, have indistinct margins, and often the only clue to their presence is a fine surface covering of yellow mucus (Fig. 1). They tend to occur in the proximal colon. With recognition of incomplete protection against proximal CRC and the molecular characteristics of interval cancers, missed sessile serrated adenomas probably underlie the failure of colonoscopy in many cases.

Other factors contributing to incomplete protection against proximal CRC include poor bowel preparation and incomplete colonoscopy. The quality of mucosal inspection is critically dependent upon mucosal cleansing, which is typically worse in the proximal colon unless some of the preparation is given within a few hours of the procedure.23 There is overwhelming evidence that bowel preparation should be ‘split’ between the day of the procedure and the night before, or taken entirely on the day of the procedure, and this is recommended in recent guidelines.34 Anaesthetic guidelines in Australia35 permit clear fluids up to 2 h prior to sedation for colonoscopy, so patients scheduled for early morning procedures do need to wake very early to complete their preparation. However, in our and others’ experience,36,37 patients are willing to comply if they understand the importance of split-dosing for mucosal cleansing, and faecal incontinence in-transit is not increased. Incomplete examination of the colon is also a potential contributor to incomplete protection, particularly if intubation of the caecum is not achieved and not recognised.38

Operator dependence of colonoscopy

Colonoscopy is an operator-dependent test, with performance characteristics that are not fixed and that vary with the endoscopist and other factors. Substantial variation between endoscopists in the detection of adenomas39,40 and sessile serrated adenomas is well recognised,31,42 with as much as a tenfold variation in adenoma detection occurring between endoscopists in the same practice. Recent studies have established an association between endoscopist and the level of protection conferred against CRC.31,44 Specifically, interval cancer rates among individual endoscopists are strongly associated with their adenoma detection rates and completion (caecal intubation) rates. The annual procedural volume of the endoscopist has not been shown to be associated with interval cancer.38

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Technological improvements

Significant improvements in endoscopic technology have occurred within the past decade. Progressive enhancements in imaging and ancillary techniques have sought to improve the capacity of colonoscopy to detect subtle precursor lesions (Fig. 4) and reduce adenoma and cancer miss rates.\textsuperscript{45,46} Technologies that have been shown to improve adenoma detection include high definition imaging, dye spray chromocolonoscopy, cap-fitted colonoscopy (application of a transparent plastic cap to the instrument tip), and repeated or retroflexed inspection in the proximal colon. However, the incremental benefits of technological improvements on adenoma detection are limited, compared with the potential benefits of reducing the variation between endoscopists.\textsuperscript{47}

Quality in colonoscopy

Addressing inadequate performance of colonoscopy is a key challenge for CRC screening programmes. It is clear that some endoscopists are capable of providing effective CRC protection and that the majority of interval CRC is preventable.\textsuperscript{6,26,44} In North America, colonoscopy by gastroenterologists compared with other doctors is associated with CRC protection in the proximal colon. Furthermore, quality audit and feedback (including quarterly report cards),\textsuperscript{46} and external review of video recordings, are known to motivate improvements in colonoscopy performance.\textsuperscript{49} This implies that variation between endoscopists can be addressed by adequate training and provider regulation.

Recognition of the variable protection afforded by colonoscopy, and its operator-dependence, has prompted international recommendations for quality improvement.\textsuperscript{50} All endoscopists are now encouraged to participate in continuous quality improvement initiatives by measuring and reporting on colonoscopy quality indicators (Table 1).\textsuperscript{31} Rates of adenoma detection and caecal intubation have been validated as powerful predictors of interval cancers after colonoscopy, and recommended minimum thresholds for these indicators have been established.

In Australia, colonoscopy quality was the focus of a report by the Quality Working Group of the NBCSP.\textsuperscript{13} This report laid the foundation for a new focus on endoscopic training in Australia\textsuperscript{52} and debate about periodic recertification of endoscopists through the submission of colonoscopy quality indicator data. Unfortunately, however, referring doctors and their patients have no source of information about endoscopists who have demonstrated the capacity to reach quality indicator standards. Furthermore, variation in colonoscopist performance is compounded by payment structures that reward volume rather than quality.\textsuperscript{47,53}

A further challenge for health services is the rational and appropriate use of colonoscopy resources. Evidence for both overuse and underuse of surveillance colonoscopy exists.\textsuperscript{35-35} The Australian National Health and...
Medical Research Council guidelines for surveillance colonoscopy following adenoma and cancer resection were recently updated, and are summarised in Table 2.56 Adherence to surveillance guidelines can be improved through local quality improvement processes.57,58 The effectiveness of colonoscopic surveillance is intimately dependent upon the quality of the baseline examination, as endoscopists with low adenoma detection rates may fail to detect significant neoplasia, recommend a longer surveillance interval, provide false reassurance to the patient and thus expose them to risks of interval malignancy. Colonoscopy performance indicators should, therefore, include both adherence to recommended surveillance interval and adenoma detection rate to motivate high-quality practice at the individual provider level.47

### Non-invasive screening tests

#### Assessment of genetic risk

Inherited genetic traits can greatly alter an individual’s risk of bowel cancer. Some of these are well understood (familial adenomatous polyposis, Lynch syndrome) and predictive genetic testing can be offered. In other cases, such as having as a first-degree relative affected under the age of 55 or two relatives affected on the same side of the family, there is a significantly increased risk but we cannot yet offer predictive testing. It is beyond the scope of this review to discuss those at high genetic risk, but it should be remembered that identifying the 2–5% of the population with these risk factors and triaging them directly to appropriate screening by colonoscopy is a very effective cancer prevention strategy.

#### Faecal occult blood testing

There are two types of faecal occult blood tests. The original is guaiac-based (gFOBT) and detects peroxidase-like activity of haem. It is inexpensive to purchase, but its interpretation is not automated or objective. In addition, dietary restriction of meat and avoidance of aspirin to minimise upper gastrointestinal bleeding have been advocated to decrease false positive results, although this is now arguable.59 There is Level 1 evidence that a programme of annual or biennial gFOBT for at least two or three rounds reduces CRC mortality by 16% (95% CI 10–22) by intention-to-treat analysis and by 25% (CI 16–22) by per-protocol analysis,11 and lasts up to 30 years.60,61 The limitation of gFOBT is its limited sensitivity for cancer and poor performance in detecting adenomas. To improve sensitivity, the faecal immunochemical test (FIT) was developed. It uses antibodies to human globin, and the analysis is automated and quantitative such that the threshold for positivity can be varied to adjust sensitivity and specificity. No dietary restrictions are required and sample collection by the participant is easier. For these reasons, randomised trials show the participation rate using FIT is 13–15% higher than that with gFOBT.59,62 There are no large scale, long-term randomised trials of

### Table 1

<table>
<thead>
<tr>
<th>Colonoscopy quality indicators adopted by the American Society for Gastrointestinal Endoscopy and the American College of Gastroenterology51</th>
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<tbody>
<tr>
<td><strong>Preprocedure</strong></td>
</tr>
<tr>
<td>1. Appropriate indication</td>
</tr>
<tr>
<td>2. Informed consent</td>
</tr>
<tr>
<td>3. Use of recommended surveillance intervals</td>
</tr>
<tr>
<td>4. Use of surveillance in UC/CD</td>
</tr>
<tr>
<td>5. Bowel preparation</td>
</tr>
<tr>
<td><strong>Intraprocedure</strong></td>
</tr>
<tr>
<td>1. Caecal intubation rate</td>
</tr>
<tr>
<td>2. Detection of adenomas in asymptomatic (screening) individuals</td>
</tr>
<tr>
<td>3. Withdrawal times</td>
</tr>
<tr>
<td>4. Biopsy specimens in chronic diarrhoea</td>
</tr>
<tr>
<td>5. Biopsy samples in UC/IBD</td>
</tr>
<tr>
<td>6. Endoscopic resection of polyps &lt;2 cm</td>
</tr>
<tr>
<td><strong>Post-procedure</strong></td>
</tr>
<tr>
<td>1. Perforation</td>
</tr>
<tr>
<td>2. Bleeding</td>
</tr>
<tr>
<td>3. Non-operative management of post-polypectomy bleeding</td>
</tr>
</tbody>
</table>

CD, Crohn disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

### Table 2

<table>
<thead>
<tr>
<th>Australian clinical practice guidelines for surveillance colonoscopy in adenoma follow up and following curative resection for colorectal cancer56</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Findings at baseline colonoscopy</strong></td>
</tr>
<tr>
<td><strong>Surveillance recommendation</strong></td>
</tr>
<tr>
<td>Follow up for patients with low-risk adenomas</td>
</tr>
<tr>
<td>One or two small (&lt;10 mm) tubular adenomas</td>
</tr>
<tr>
<td>Follow up for patients with high-risk (advanced) adenomas</td>
</tr>
<tr>
<td>Three or more adenomas</td>
</tr>
<tr>
<td>Advanced adenoma (any ≥10 mm, with tubulovillous or villous histology, or with high-grade dysplasia)</td>
</tr>
<tr>
<td>Follow up for patients with multiple numbers of adenomas</td>
</tr>
<tr>
<td>Five or more adenomas</td>
</tr>
<tr>
<td>10 or more adenomas</td>
</tr>
<tr>
<td>Following resection for colorectal cancer</td>
</tr>
<tr>
<td>Post-surgical resection</td>
</tr>
<tr>
<td>Perioperative or 1-year colonoscopy shows advanced adenoma</td>
</tr>
<tr>
<td>Perioperative or 1-year colonoscopy normal or only 1–2 non-advanced adenomas</td>
</tr>
</tbody>
</table>

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FIT, but there is consensus that it should replace gFOBT as the faecal occult blood test of choice. Cross-sectional studies with colonoscopy as the reference standard show that FIT detects cancer or advanced adenomas at least three times more frequently than gFOBT. In a study of 1256 participants who had not been previously screened and who underwent both FIT and colonoscopy, FIT detected seven of eight cancers and 38 of 111 advanced adenomas. In this study, FIT was positive in 10% of participants, and 37% of these had advanced adenomas or cancer. Advanced adenomas or cancer were found in 6.5% of participants who were FIT-negative. In the Australian context, cancer is found in 4.3% and advanced adenoma in 23% of participants with a positive FIT in the NBCSP in which FIT was positive in 7.7% of participants. To achieve this, the FIT cut-off was set such that 7.5% were positive and required colonoscopy. The stage of cancers detected through the NBCSP has been examined as a surrogate marker for the effect on CRC mortality and significant shift to earlier stage disease demonstrated.

There are many commercial FIT tests available, and often there are limited data regarding their performance characteristics. For example, there is limited, temperature-dependent stability once the faecal sample has been added to the kit, and it has been observed that the rate of positivity declined during the Australian summer. Monitoring of the NBCSP enabled the detection of this effect and the kit has since been modified, but such effects may not be detected outside such a programme.

**Computed tomography (CT) colonography**

The attractive characteristics of CT colonography are its >90% sensitivity for cancer and polyps >1 cm and its relatively non-invasive nature. The protocol includes laxative-free bowel preparation with administration of an oral contrast agent and bowel distention through anal insufflation of carbon dioxide without sedation. If there are positive findings, colonoscopy is required. However, it was not approved for CRC screening in the USA based on concerns that for its cost it did not detect small or flat polyps, such as sessile serrated adenomas, and that there were risks from radiation exposure and the subsequent investigation of incidental extracolonic abnormalities. Like colonoscopy, the quality of CT colonography is operator-dependent. In a randomised population based trial, the uptake of CT colonography was significantly higher than colonoscopy (34% vs 22%), although neither was very high. When the burden of the screening test was assessed after the event, participants reported CT colonography to be more burdensome particularly due to bowel distention without sedation and subsequent disturbed bowel habit. Advances that require less bowel preparation and distention, and that use magnetic resonance rather than radiation, may make medical imaging a more attractive option in the future. Certainly, CT colonography should already be used in place of double-contrast barium enema in patients unable to undergo colonoscopy.

**Faecal DNA testing**

There is a strong rationale for basing a test on specific genetic changes, including mutations in genes controlling the WNT and MAPK pathways, such as Kras and APC, and methylation of particular genes, since these are present in the neoplastic cells of polyps and cancers that are shed directly into the lumen of the bowel. There has been an enormous amount of research in this field, and some tests have been marketed and endorsed for use in the USA. The cost of several hundred dollars remains a barrier, although this is likely to decrease with rapid improvements in technology. In most instances, the faecal DNA tests have been assessed in highly selected groups of patients who have had colonoscopy demonstrating a cancer or large polyp or no pathology at all. The most promising tests have sensitivity for cancer of >85% and for large adenomas of >50% in such case-control studies, but these need to be assessed in the screening setting with average-risk, asymptomatic people over 50. A multi-target faecal DNA test was recently compared with FIT in average-risk screening and found to have a sensitivity of 92.3% for CRC, 42.4% for advanced lesions and 42.4% for sessile serrated adenomas 1 cm or greater. Sensitivity was consistently approximately 20% higher than the FIT comparator for each category of lesion, although false positive rates were higher.

**Horizon scanning of new technology**

There would be many advantages of having a blood test for CRC screening as specimens would be simple to collect and process. One of the more promising strategies is based on the discovery that DNA originating in cancer cells can be found in the plasma. Some genes are heavily methylated in virtually all polyps and cancers not just those arising through the serrated pathway and this can be assessed fairly simply in plasma DNA. Methylation of septin-9 (SEPT9) appears to be a promising marker and is under evaluation in the screening setting.

Capsule colonoscopy is an attractive option, being safe, non-invasive and resulting in direct visualisation. Challenges include poor visualisation of parts of the bowel due to the large diameter and speed of transit, the need for excellent bowel preparation, and the cost of the device.
Flexible sigmoidoscopy

Flexible sigmoidoscopy is the only screening strategy apart from gFOBT with Level 1 evidence to support it. Four population-based, prospective, randomised controlled trials of once off flexible sigmoidoscopy have shown a 22–31% reduction in CRC mortality on intention-to-treat analysis. The reduction in mortality is confined to distal cancers within the reach of the sigmoidoscope, and this is a significant limitation to the acceptability of the test especially considering its invasive nature and the resources needed to provide it. The participation rate is relatively low at 33% or less in most studies, and in the Australian setting has been found to be 15.5%.

Improving screening in Australia

FIT offered biennially as part of a regular programme is effective for CRC screening, and randomised controlled trials of screening colonoscopy are underway. Colonoscopy at more frequent intervals is clearly indicated in individuals who are above-average risk because of a strong family history or previous polyps or cancer. Rather than continuing to debate which is the ‘best’ test currently available, a more fruitful approach may be to acknowledge that there is a choice of screening methods and focus on the goal of improving overall participation rate and being able to measure this. Apart from the resources needed to provide it, the limitation of colonoscopy is that many average-risk patients are not prepared to undergo it, with participation rates in the order of 25–38% compared with participation rates of 67–62% for FIT among the same population. However, it is clear that at a single point of time, colonoscopy is more accurate than FIT, and some participants and doctors have a very strong preference for it. Offering a choice of screening test to randomly selected Australians did not improve participation, but this study showed that significant numbers of invitees had already undergone colonoscopy in the preceding 5 years. Some of these colonoscopies were likely done for screening, and it seems most efficient to acknowledge this choice and not rescreen these people.

 Apart from the limited NBCSP, screening in Australia is opportunistic, and there are few ongoing data to measure the screening rate even to know how we compare with international benchmarks and assess equity of access. The power of organised screening with a risk- and preference-based approach taking advantage of electronic medical records is exemplified by the results of the Kaiser Permanente programme. In addition to opportunistic referral for colonoscopy for screening and other valid reasons, electronic medical records are used to identify persons not up to date by this approach and target them for an organised population-based mailed outreach of FIT screening kits. Since this organised screening commenced in 2007, the proportion of the population screened according to guidelines has increased from 37% to 79% (commercially insured) and from 41% to 91% (Medicare), and there has been a decrease in cancer stage and incidence. The importance of a comprehensive information system coordinating care and facilitating quality assurance has been emphasised in many national programmes. Better data would allow rational allocation of resources and may in itself drive improvements.

References

Leggett & Hewett


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REVIEW

Portal hypertension: pathophysiology, diagnosis and management

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Abstract

Portal hypertension is an important complication of liver disease. As a result of elevated pressures within the portal vein several complications can arise, including the development of oesophageal and gastric varices, ascites, hepatic encephalopathy as well as complications secondary to circulatory dysfunction, such as hepatorenal syndrome, portopulmonary syndrome and hepatopulmonary syndrome. This review outlines the pathogenesis and diagnosis of portal hypertension and outlines the management of these various important clinical sequelae. The management of oesophageal and gastric varices is particularly important, and both the emergency management together with prophylactic management of this condition are described.

Introduction

Many of the clinically significant complications of cirrhosis arise as a consequence of increased portal hypertension (PHT). This is defined as hepatic venous pressure gradient (HVPG) greater than 5 mmHg, with complications arising once this exceeds 10 mmHg. Portal hypertensive complications are associated with high morbidity and mortality and include variceal bleeding, portal hypertensive gastropathy, ascites and hepatic encephalopathy. These conditions present a challenge to the Australian health system with the economic costs associated with treating liver disease estimated to be higher than that of type 2 diabetes and chronic kidney disease combined. Over the past decade, our understanding of portal hypertension has increased dramatically allowing for optimisation of management and new therapeutic approaches.

Portal hypertension pathophysiology

The portal vein acts as the major outflow tract for the splanchnic circulation. The portal system is a low pressure, low resistance system. In the healthy state, considerable post-prandial increases in portal venous blood flow do not significantly alter portal pressure due to the highly compliant nature of this system. The normal portal vein pressure is 5 mmHg or less and is a product of blood flow (Q) and resistance (R) according to Ohm’s law:

$$\text{Portal Pressure} = Q \times R$$

The aetiology of increased portal resistance is commonly categorised according to anatomical location into pre-hepatic, intra-hepatic and post-hepatic causes (Table 1). In the western world, sinusoidal PHT secondary to cirrhosis is the most common cause of PHT.

In cirrhosis, the architectural changes associated with fibrosis and nodule formation result in a fixed alteration to sinusoidal blood flow. In contrast to this fixed hepatic resistance, there is a dynamic component which arises from contraction of myofibroblasts within the space of Disse. These myofibroblasts originate from hepatic stellate cells, which in the healthy state are the predominant storage site for vitamin A. In the presence of inflammation, cytokines released from injured hepatocytes stimulate the recruitment and transdifferentiation of hepatic stellate cells into contractile myofibroblasts with the capacity to deposit collagen. An excess of locally produced vasoconstrictor peptides together with a relative depletion in hepatic nitric oxide

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(NO) contribute to this dynamic component of hepatic resistance. These reversible components may represent up to 30% of the total resistance to portal blood flow.

The increased pressure within the portal venous system induces shear stresses in the splanchnic vessels, and together with translocation of bacterial lipopolysaccharides results in excessive systemic NO production. The subsequent systemic vasodilatation activates several homeostatic regulatory systems, such as the renin-angiotensin-aldosterone system (RAAS) and antidiuretic hormone (ADH) causing sodium and water retention. These events result in an increase in splanchnic vasodilation and blood flow with resultant increase in flow into the portal venous system further exacerbating PHT.

**Detection of portal hypertension**

The presence of portal hypertension may be clinically silent; however, findings such as splenomegaly, ascites and abdominal wall collaterals (caput medusae) strongly suggest its presence. Radiological imaging, such as Doppler ultrasound and computed tomography may demonstrate the presence of collateral vessels, alterations in portal venous flow, splenomegaly and ascites, thereby supporting the diagnosis of portal hypertension. Despite this, the first presentation of portal hypertension may be with variceal haemorrhage, and this needs to be urgently excluded in any patient with suspected liver disease who has significant gastrointestinal haemorrhage.

Direct measurement of portal venous pressures is invasive and requires significant procedural experience. This technique involves the introduction of a balloon catheter through the jugular or femoral vein into the hepatic vein. The HVPG is derived from subtracting free hepatic vein pressure (FHVP) from wedge hepatic vein pressure (WHVP):

\[ \text{HVPG} = \text{WHVP} - \text{FHVP} \]

PHT is defined by an HVPG > 5 mmHg. Clinically significant PHT is defined as an HVPG ≥ 10 mmHg. This threshold is required for the development of complication of PHT, such as porto-systemic collaterals, varices, ascites and circulatory dysfunction. Variceal haemorrhage is associated with HVPG greater than 12 mmHg and when HVPG is greater than 20 mmHg following variceal haemorrhage, the risk of death increases fivefold. Likewise, the risk for development of hepatocellular carcinoma increases to sixfold when the HVPG is >10 mmHg.

The routine use of HVPG in clinical practice is generally limited to specialist centres. The role that less invasive methods of predicting PHT, such as liver stiffness measurement (LSM) using transient elastography, is yet to be established. The ideal LSM to determine significant PHT requires further validation; however an LSM of >20 kpa appears to have a high specificity (92.3%), while an LSM > 13 kpa has a high sensitivity for PHT (94%). The use of a ratio of spleen size and platelet count in combination with LSM may overcome these limitations with recent literature demonstrating a combined sensitivity and specificity greater than 80% for detection of significant PHT.

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Complications of portal hypertension

Gastrointestinal haemorrhage

Oesophageal varices

Oesophageal varices are present in 40% of patients with an initial diagnosis of Child–Pugh A cirrhosis and in 60% of patients with signs of decompensation.\textsuperscript{10,11} Those without varices at initial assessment develop them at an incidence of 7% per year.\textsuperscript{11} Seven per cent of small varices (<5 mm) will bleed over a 2-year period compared with 30% of large varices.\textsuperscript{11} The risk of subsequent haemorrhage is determined by the degree of underlying hepatic dysfunction, size of varices and presence of high-risk stigmata at endoscopy.

Primary prophylaxis The treatment of varices before a bleeding episode has occurred is referred to as primary prophylaxis (Fig. 1). It is recommended to perform a gastroscopy to determine the presence and size of oesophageal or gastric varices at the time of diagnosis of cirrhosis or at the time of new onset hepatic decompensation. In those with absent or only small varices, biennial surveillance is recommended. Non-selective beta blockade (NSBB) does not appear to prevent variceal development,\textsuperscript{12,13} but may be used in patients with large varices or those with stigmata associated with high bleeding risk, as an alternative to endoscopic variceal band ligation (EVBL). NSBB reduce portal pressure by reducing cardiac output and splanchnic vasodilatation (Table 2). At 2 years, the bleeding risk is reduced from 25% to 15%, with a reduction in mortality from 27% to 23%.\textsuperscript{10} The doses are typically aimed at reducing the resting pulse rate by 25% or to 55 b.p.m.; however, only 30–40% of patients reduce HPVG by the recommended 20% or to <12 mmHg.\textsuperscript{16} The combination of nitrates and NSBB
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Indication</th>
<th>Dosage</th>
<th>Evidence</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propanol</td>
<td>Reduces portal vein blood flow and pressure by:</td>
<td>1) Primary prophylaxis in patient with oesophageal varices &gt;5 mm</td>
<td>10 mg twice daily titrated to maximal tolerated dose</td>
<td>Primary prophylaxis</td>
<td>Fatigue, Lethargy, Postural hypotension, Refractory ascites, Bronchospasm, Impotency, Nightmares</td>
</tr>
<tr>
<td></td>
<td>• Reduced cardiac output (β1 blockade)</td>
<td>2) Secondary prophylaxis for recurrent variceal haemorrhage</td>
<td>Aim for reduction of heart rate by 25% or resting heart rate of 55 bpm</td>
<td>10% reduction in 2 year bleeding risk&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Reduced splanchnic vasodilation (β2 – blockade)</td>
<td>3) Secondary prophylaxis for Portal Hypertensive Gastrophy</td>
<td></td>
<td>4X 2 year Mortality reduction&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
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<td>Secondary prophylaxis</td>
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<td>40% decrease in re-bleeding&lt;sup&gt;10&lt;/sup&gt;</td>
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<td></td>
<td>Mortality reduction of 25%&lt;sup&gt;10&lt;/sup&gt;</td>
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<tr>
<td>Carvedilol</td>
<td>1) α1 blockade reducing intra-hepatic resistance</td>
<td>Secondary Prophylaxis for recurrent variceal haemorrhage</td>
<td>6.25 mg titrated to blood pressure and heart rate (55 bpm or 25% reduction)</td>
<td>• Improved proportion meeting HVPG targets compared with NSBB (50% v 16% P &lt; 0.05)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Greater decrease in mean arterial pressures than NSBB (11% v 5%)&lt;sup&gt;14&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>2) NSBB (as above)</td>
<td></td>
<td></td>
<td>Possibly lower rates of first variceal bleeding compared with EBVL (10% v 23%)&lt;sup&gt;14&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Greater decrease in mean arterial pressures than NSBB (11% v 5%)&lt;sup&gt;14&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>Systemic and splanchnic vasodilation reduces portal blood flow</td>
<td>Not currently recommended in primary or secondary prophylaxis</td>
<td>10 mg nocte titrated to blood pressure (&gt;95 mmHg systolic)</td>
<td>Reduces HVPG when added to NSBB</td>
<td>Hypotension, Increase 6-year mortality</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Splanchnic vasoconstriction and inhibition of vasodilator peptides (glucagon) release</td>
<td>Management of acute suspected or proven variceal haemorrhage</td>
<td>50 mcg bolus followed by 50 mcg/h infusion for 2–5 days</td>
<td>• Improved haemostasis (80%) at time of endoscopy</td>
<td>Minimal, Tachyphylaxis</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>Splanchnic vasoconstriction reducing portal blood flow</td>
<td>1) Management of acute suspected or proven variceal haemorrhage</td>
<td>1–2 mg IV per 4–6 hourly for 24 h and reduced to 1 mg 4 hourly</td>
<td>Reduced re-bleeding rates</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>and reduced to 1 mg 4 hourly</td>
<td>Increased haemostasis (80%) at time of endoscopy&lt;sup&gt;19&lt;/sup&gt;</td>
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<td></td>
<td>Total treatment of 2–5 days</td>
<td>Reduced all cause mortality (RR 0.65 CI 0.49–0.88)&lt;sup&gt;19&lt;/sup&gt;</td>
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<td></td>
<td>Hepatorenal</td>
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<td></td>
<td></td>
<td>• Improved creatinine and urine output</td>
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<td></td>
<td></td>
<td></td>
<td>• No effect on mortality</td>
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</tr>
</tbody>
</table>

EBVL, endoscopic variceal band ligation; HVPG, hepatic venous pressure gradient; NSBB, non-selective beta blockade; RR, relative risk.
reduces HVPG, but without any additional reduction in mortality or haemorrhage rate compared with NSBB alone. Carvedilol may be more effective at reducing portal pressure and has shown superiority to EVBL for primary prevention. However, worsening of resistant ascites and hypotension limits widespread use. Unfortunately, the dose of NSBB required to reduce portal pressure adequately may lead to unacceptable fatigue, dizziness and shortness of breath, symptoms that contribute to a 15% discontinuation rate. EVBL appears equivalent to NSBB for primary prophylaxis, with importantly no difference in survival between the two strategies. Thus, the choice between NSBB and EVBL is highly dependent on available resources as well as patient tolerance and compliance with pharmacological therapy.

**Acute variceal haemorrhage** Following an acute variceal haemorrhage, spontaneous cessation of bleeding occurs in 40–50%, presumably secondary to hypovolaemia and subsequent splanchnic vasoconstriction. Excessive transfusion may elevate portal pressure and a restrictive transfusion protocol, aiming for haemoglobin of 80 g/L has demonstrated improved survival and decreased re-bleeding in Child–Pugh A and B patients.

Management of coagulation dysfunction can be challenging. Elevation in international normalised ratio (INR) is an important measure of hepatic dysfunction. However, it is now well recognised that in cirrhosis there is dysregulation of both prothrombotic and anti-thrombotic systems. This reduces the predictive value of INR for bleeding tendency in these patients. Typically, correction of coagulation abnormalities requires the administration of fresh frozen plasma (FFP) and prothrombinex. The volume expansion associated with these products has the potential to increase portal pressure and trigger re-bleeding. Furthermore, significant amounts of FFP are required to correct INR in cirrhotic patients without any evidence for benefit. Correction of platelet count to greater than 70 × 10^9/L appears sufficient to control bleeding, whereas counts > 50 × 10^9/L are thought to be safe for invasive procedures. Due to a lack of evidence regarding efficacy, excessive correction of coagulation abnormalities should be discouraged.

The use of short-term antibiotics following variceal haemorrhage, with or without ascites, has been shown to improve mortality through decreased rates of re-bleeding and spontaneous bacterial peritonitis (SBP). In the setting of severe liver disease, evidence supports the use of ceftriaxone 1g intravenously daily. Antibiotics should be commenced on presentation and continued for a period of 7 days. Switching to an oral quinolone antibiotic may be appropriate once the patient is stable (Table 3).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Acute and prophylactic antibiotics in portal hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td><strong>Mechanism of action</strong></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Gram-negative bactericidal agent</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Gram negative bacteriostatic agent</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethizole</td>
<td>Broad spectrum bacteriostatic agent</td>
</tr>
</tbody>
</table>

SBP, spontaneous bacterial peritonitis.
The vasoactive agents, terlipressin and octreotide play a major role in controlling acute oesophageal variceal haemorrhage. These agents can achieve initial haemostasis in 60–80% of cases. Terlipressin reduces portal pressure through splanchnic vasoconstriction. The intact molecule causes immediate vasoconstriction, followed by a delayed effect due to enzymatic breakdown of terlipressin into vasopressin. Terlipressin is the only vasoactive agent that has been demonstrated to decrease mortality in acute variceal haemorrhage on meta-analysis and is generally given for a minimum of 5 days. Caution should be taken in individuals with vascular disease because of potential to cause ischaemia. Octreotide, a somatostatin analogue, has inhibitory effects on exocrine and endocrine hormones and decreases portal pressures. In combination with EVBL there is evidence suggesting equivalent efficacy of octreotide and somatostatin to terlipressin on re-bleeding rates, transfusion requirement and mortality (8.8% vs 8.9% vs 8.0%, respectively; \( P = 0.929 \)).

Timely definitive endoscopic treatment is recommended with significant benefits in regards to re-bleeding and mortality. Failure to proceed to endoscopic treatment within 15 h is associated with higher mortality. A meta-analysis of 10 randomised controlled trials demonstrated that EVBL was superior to sclerotherapy in controlling bleeding (RR 0.53 CI 0.28–1.01.). Failure to control bleeding or lack of available expertise may require balloon tamponade through insertion of a Sengstaken–Blakemore tube or equivalent, until more definite treatment is available. Tamponade can control bleeding in over 80% of patients, but is associated with a risk of aspiration and perforation. Initial HVPG measurement greater than 20 mmHg predicts those at increased risk of early and late re-bleeding. Initial treatment failure can be managed with repeat endoscopic treatment or transjugular intra-hepatic portosystemic shunt (TIPS) (Fig. 2). TIPS in this setting decreases bleeding rates, however, it appears to have no effect on long-term survival and is associated with increased rates of encephalopathy. The early use of TIPS in a select group of patients with severe liver disease (Child–Pugh B or C), who have endoscopically confirmed variceal haemorrhage, may improve the prognosis and shorten the acute hospital stay compared with a more conventional combination of pharmacotherapy and EVBL.

Secondary prophylaxis Mortality from an initial haemorrhage is as high as 80% within the first year with an associated mortality of 33%. Severe initial bleeding, as defined by active bleeding at endoscopy, haemoglobin less than 80 g/L and gastric variceal bleeding, is associated with increased re-bleeding rates.

Secondary prophylaxis is the management of varices following an index bleed. Management comprises EVBL and NSBB. NSBB has been demonstrated to reduce re-bleeding by 40% with a reduction in mortality of 25%. On meta-analysis of 23 randomised controlled trials, combination therapy was associated with a significantly lower rate of re-bleeding (12% reduction) and recurrence (RR 0.64 CI 0.53 to 0.77) compared with EVBL alone. EVBL should be repeated until varices are eradicated, which typically requires three to five sessions. Ongoing surveillance is recommended on a 3 to 6 monthly basis thereafter. Combination therapy with nitrates and NSBB is associated with improved mortality; however, high rates of discontinuation secondary to side-effects. Nitrate alone may be associated with higher long-term mortality particularly in those over 50 years of age. The use of TIPS for secondary prophylaxis reduces re-bleeding events by 28% compared with endoscopic therapy alone. However, there is increased morbidity secondary to encephalopathy and no clear survival benefit.

Gastric varices

While less common and associated with lower rates of bleeding compared with oesophageal varices (25% vs 64%), haemorrhage associated with gastric varices is often more severe with increased transfusion requirements and higher re-bleeding rates. Gastric varices can be classified by anatomical location (Fig. 3). This classification can assist the prediction of bleeding and directs treatment strategies. Pharmacological therapy of gastric varices is identical to that of oesophageal varices (Table 2). Gastro-oesophageal varices (GOV) 1 are considered extensions of oesophageal varices and can be treated in a similar fashion. Isolated gastric varices (IGV) 1 are less common, but are more likely to bleed, whereas IGV2 rarely bleed. Endoscopic therapy of non-GOV 1 varices utilises tissue adhesives injected directly into the lesion. Tissue adhesives are preferred given the superiority in reducing long-term re-bleeding rates (24% reduction). Risks associated with tissue adhesives are systemic emboli with reports of splenic infarction, pulmonary emboli and cerebral strokes. Only three studies have compared tissue adhesives with TIPS demonstrating equal control of initial haemorrhage, but favouring TIPS in the prevention of re-bleeding. NSBB are less effective than tissue adhesives for secondary prophylaxis.
Portal hypertensive gastropathy

Portal hypertensive gastropathy (PHG) is characterised by the endoscopic appearance of ‘snake scale’-like mucosal changes in the stomach. Rarely does it present with acute gastrointestinal haemorrhage (2.5%), but it can be a cause of chronic anaemia (10%) in cirrhosis. While requiring PHT, it does not appear to be directly correlated to the severity of PHT, the degree of underlying liver disease or presence of oesophageal varices. The pathology of PHG is incompletely understood, but appears to result from a combination of alteration in gastric blood flow, hypoxia and impairment of gastric mucosal defences. Long-term NSBB reduces recurrent bleeding, and vasoconstrictive therapy appears to be effective in acute bleeding episodes. TIPS may be beneficial with one study demonstrating a reduction in incidence of 90%, but data are limited.

Haemodynamic complications of portal hypertension

Ascites

Ascites is the accumulation of fluid in the peritoneal cavity and occurs in 50% of cirrhotic patients within 10 years. As a consequence of the vasodilatory and a hyperdynamic circulatory response to PHT, the RAAS

Figure 2 Acute management of variceal haemorrhage.
and ADH drive inappropriate retention of salt and water. In the setting of hypoalbuminaemia, it has been postulated that excessive volume leaks directly from the splanchnic capillaries and the hepatic sinusoids. Abdominal ultrasound can demonstrate even a small volume of ascites, whereas moderate accumulation of fluid can be confirmed by clinical examination alone. Diagnostic paracentesis is recommended with the initial presentation of ascites or if clinical deterioration suggests SBP. Analysis of the serum ascites albumin gradient (SAAG) has replaced the use of protein concentration for determination of aetiology. A SAAG equal to or greater than 11 g/L is diagnostic of PHT-related ascites with an accuracy of 97%. SBP may present with worsening hepatic encephalopathy, sudden onset of abdominal pain and fever. Polymorphonuclear count can be used to confirm the presence of SBP with counts greater than 250/mm³ being diagnostic. If SBP is confirmed, treatment is initiated with a third generation cephalosporin until further antibiotic sensitivities are known. Aminoglycosides should be avoided given the risk of renal impairment. Four randomly controlled trials support the use of albumin in SBP with a reduction in renal failure (22% reduction) and mortality (19.4% reduction). It is recommended that patients receive 1.5 g albumin/kg within 6 h of presentation and 1 g/kg on day 3. Daily norfloxacin or trimethoprim/sulfamethoxazole is recommended prophylaxis for those with prior episodes of SBP (Table 3).

Dietary salt restriction to less than 2000 mg/day appears to be effective in only 10% of patients. Comonly, patient will accept additional medication rather than further dietary salt reduction. Caution should be taken when using NSBB in these patients because of increasing evidence suggesting a worse survival in the setting of resistant ascites. NSBB should be ceased in patients who have SBP as there is an associated reduced survival in this cohort. Angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs should be avoided to prevent worsening renal function. Spironolactone and furosemide are recommended diuretic therapies. In isolation, spironolactone is more effective with more controlled weight loss, but at the risk of hyperkalaemia. The addition of furosemide allows better sodium excretion with control of serum potassium concentration. Doses of 100 mg of spironolactone and 40 mg of furosemide can be safely initiated, with maximal doses of 400 mg and 160 mg respectively. Spironolactone may not be tolerated because of painful gynaecomastia, and in these instances amiloride may be substituted. Compliance and titration of dose can be monitored through assessment of 24 h urinary sodium or conveniently by a spot ratio of [Na⁺]/[K⁺] > 1.41 Diuretics should be ceased in the setting of severe renal impairment or severe hyponatraemia (<120 mmol/L). Diuretic intolerant or resistant patients can be managed with regular paracentesis or can be considered for TIPS.

Hepatorenal syndrome

Hepatorenal syndrome (HRS) is defined by marked reduction in renal function in the presence of cirrhosis complicated by ascites in the absence of other causes. Alterations in renal blood flow are thought to be the precipitating event. This results in a reduction in glomerular filtration rate and sodium and water retention. The syndrome itself is characterised by oliguria, low urinary sodium output (<20 mmol) and hyponatraemia. Hepatorenal syndrome is classified as type I HRS, when there is rapid deterioration of renal function over a 2-week period and type II HRS when onset is more prolonged. Type I is typically associated with a precipitating factor, such as SBP, large volume paracentesis without albumin replacement or gastrointestinal bleeding.

The diagnosis of HRS is one of exclusion requiring cessation of nephrotoxic agents, treatment of possible underlying infection and hypovolaemia. Albumin replacement is recommended initially at a dose of 1 gram per kilogram for a 48-h period. Terlipressin is recommended following failure of volume expansion at 1–2 mg 4–6 hourly. Prognosis of Type I HRS is poor in the absence of liver transplantation with only 10% leaving hospital.
Hepatopulmonary/portopulmonary syndromes

Hepatopulmonary syndrome is characterised by a triad of portal hypertension, pulmonary vasodilation/shunting and impaired oxygenation as defined by a widened A-a gradient. The pathophysiology, while not completely understood, involves excessive NO and Endothelin-1 production secondary to inflammation from hepatic injury and translocation of gastrointestinal bacteria.43 Clinical features can include clubbing and platypnea-orthodeoxia (dyspnoea and deoxygenation induced by upright posture). Mortality arises from liver failure rather than hypoxia. In the absence of liver transplantation, survival at 5 years is 23%.43 Portopulmonary syndrome refers to pulmonary hypertension in the presence of PHT without alternative causes. Traditional therapies for pulmonary hypertension may have benefit, but liver transplantation can be curative.

Hepatic encephalopathy

Hepatic encephalopathy is a neuropsychiatric complication of PHT. Through the development of collateral vessel and obstruction of hepatic blood flow, neuroactive peptides are shunted in the systemic circulation rather than detoxified by the liver. Theories suggest ammonia, inflammatory cytokines and hyponatraemia act synergistically resulting in cerebral oedema, astrocyte swelling and alternations in astrocyte mitochondrial function.44 The severity of presentation, classified by the West Haven criteria (Table 4), can range from subtle alterations in mood to overt coma. Biochemical measurement of ammonia to diagnose encephalopathy is debatable given the fact that this condition relies on clinical diagnosis and can occur in the absence of elevated ammonia levels. Initial therapy should be aimed at correcting possible aetiologies, such as infection, electrolyte imbalances (such as hypokalaemia) and gastrointestinal bleeding. Current therapies target the absorption and production of ammonia. Lactulose alters gastrointestinal pH favouring lactobacilli over urease-containing bacteria and enhances production of non-absorbable ammonia. Furthermore, these laxatives enhance faecal nitrogen excretion.44 In small placebo studies, lactulose appeared more effective in controlling hepatic encephalopathy and preventing recurrent episodes, but had no effect on mortality.44 Dosing is generally titrated to the number of bowel action aiming for two to three loose actions, although there is little evidence to support this. In the comatose patient, nasogastric administration or 200 mL enemas of lactulose may be required.

Neomycin was the first antibiotic to demonstrate effectiveness in hepatic encephalopathy, but its use has been limited because of ototoxicity and nephrotoxicity.44 Rifaximin (550 mg BD), a minimally absorbable oral antibiotic is currently available in Australia for use in lactulose resistance encephalopathy. When used in conjunction with lactulose, rifaximin has been shown to reduce recurrent encephalopathy and hospitalisation.45

Conclusion

The management of PHT has improved dramatically over the past decade. This improvement has come on the background of technical advancements and enhanced understanding of the pathophysiology. Future therapies will target additional pharmacological sites not yet utilised. Endothelial receptor blockade appears promising in animal models of pre- and intra-hepatic PHT; however, further human studies are required. Statins are thought to increase NO synthase selectively in the liver, limiting the systemic side-effects that hamper nitrate use. Preliminary data have demonstrated a statistical significant increased survival in Child–Pugh A and B patients presenting with variceal haemorrhage.11 Blockade of angiotensin-mediated hepatic vasoconstriction and fibrosis can reduce HVPG, however, the effects appear equivalent to NSBB and are non-additive with increased renal impairment and hypotension common as liver function worsens. Ultimately addressing the cause of PHT and prevention will be the most effective therapy.
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**ORIGINAL ARTICLES**

**Blood oxygen equilibration time after cessation of supplemental oxygen in chronic respiratory disease**

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**Key words**

hypoxaemia, chronic respiratory disease, arterial blood gas, supplemental oxygen, oximetry.

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**Abstract**

**Background:** Measurement of the arterial partial pressure of oxygen (PaO₂) while breathing air is an informative investigation in patients with hypoxaemia due to chronic respiratory disease, but there are a lack of published data on the time needed for blood oxygen levels to equilibrate after cessation of supplemental oxygen (O₂) in such patients.

**Aim:** To determine the blood oxygen equilibration time after cessation of O₂ and thereby provide guidance on best timing of baseline arterial blood gas analysis in this population.

**Methods:** Medically stable subjects with chronic respiratory disease were administered O₂ at a constant concentration. Continuous pulse oximetry was recorded from before cessation of O₂ to beyond the point of oxygen saturation (SpO₂) equilibration. Data were fitted to an exponential decay model. Blood oxygen equilibration time was defined as the t₉₀, the time taken for SpO₂ to fall 90% of the difference between initial (on O₂) and final (on air) values.

**Results:** Eighty-two (82) subjects with a mean age of 66 years were included. The largest diagnostic category was chronic obstructive pulmonary disease (37), followed by interstitial lung disease (15) and bronchiectasis (12). The median t₉₀ was 6 min 18 s (interquartile range: 4 min 32 s–10 min 30 s). The 95th centile t₉₀ value was 20 min.

**Conclusion:** In the majority of patients with chronic respiratory disease, a time delay of 20 min between cessation of supplemental O₂ and PaO₂ measurement allows confidence that the result is a true baseline value.
Introduction

In patients with chronic respiratory disease, arterial blood gas (ABG) analysis while breathing air is a common investigation to determine the degree of hypoxaemia, particularly when the need for domiciliary supplemental oxygen (O2) is being assessed. Often, at the time this test is planned, such patients are already on supplemental O2. This must be ceased prior to blood sampling in order to allow the arterial partial pressure of oxygen (PaO2) to fall to its baseline value.

The time delay between cessation of O2 and blood collection is an important factor in attaining an accurate baseline PaO2 value. If the test is performed before blood oxygen has reached its new steady state, a misleadingly high PaO2 will result. However, there is a surprising paucity of published data to guide clinicians on the optimal timing of ABG analysis in this scenario.

In 1962, Massaro et al. reported effects of O2 administration by different means on ABG measurements in 15 adult males with chronic obstructive pulmonary disease (COPD) and respiratory acidosis.1 Ten subjects had data collected after cessation of O2. Return of PaO2 to pre-O2 administration levels occurred within 20–30 min in nine subjects and took 40 min in one.

In 1975, Sherter et al. reported a time of 20–25 min to PaO2 equilibration in a group of nine men with moderate to severe COPD after cessation of 100% O2.2 The authors recommended that measurement of PaO2 should be delayed for more than 25 min after stopping supplemental O2 in patients with COPD. At the same time, Howe et al. published contrasting results in a different population. In a group of 21 subjects with various cardiac diseases and no respiratory disease, PaO2 equilibration occurred within 5–7 min.3 Naughton et al. found that PaO2 equilibrated within 5 min in nine patients with COPD undergoing normobaric and hypobaric hypoxia altitude simulation tests.4 Studies by Solis et al.5 and Fildissis et al.6 assessed the time to PaO2 equilibration after reductions or increases in fraction of inspired oxygen (FiO2) in critically ill, mechanically ventilated patients. The former included seven patients with diffuse pneumonia in whom equilibration occurred within 10 min. The latter included 40 patients with diverse diagnoses. For a 30% decrease in FiO2, PaO2 equilibration occurred within 5 min.

Of the above studies, only the one conducted by Sherter et al. was focused on providing direction on the best timing of PaO2 measurement after stopping O2 in patients with stable chronic respiratory disease. However, there were very few subjects, and the protocol of administration of 100% oxygen does not simulate routine clinical practice.

The aim of this study was to determine the blood oxygen equilibration time in adults with hypoxaemia due to chronic respiratory disease and thereby provide a guide on the optimal time delay between cessation of supplemental O2 and arterial blood sampling for valid baseline PaO2 assessment in this population.

Methods

Subjects

This study received approval from the Ethics Review Committee (Royal Prince Alfred Hospital Zone) of the Sydney South West Area Health Service (protocol number X10-0221). Adult inpatients and outpatients of a Sydney tertiary referral hospital with resting hypoxaemia due to any chronic respiratory disease were included after giving written informed consent. Hypoxaemia was defined as a SpO2 of 94% or below when breathing air. This threshold was chosen to allow analysis of patients with hypoxaemia ranging from mild to severe. Eligibility for the study required that the treating physician deemed the patient’s condition to be stable. For inpatients, measurements were made towards the end of the hospital admission after resolution of the recent acute medical problem. Diagnostic categories were defined according to the diagnosis made by the treating respiratory physician.

Measurements

Changes in finger pulse oximetry were used as non-invasive surrogate measurements of changes in PaO2 to ensure adequate time resolution of data and patient acceptability. Supplemental O2 at a constant flow rate was administered through a Venturi mask for at least 30 min with the subject at rest. FiO2 was selected as deemed appropriate for each clinical case and in such a way to simulate common practice. We ensured that the FiO2 was sufficient to avoid significant oxygen desaturation at the start of the protocol and avoided high FiO2 and high saturations in those known to be hypercapnic. A Masimo Radical 9 Signal Extraction Technology oximeter (Masimo, Irvine, CA, USA) was used to record SpO2 continuously from at least 30 s before cessation of O2 until at least 2 min beyond the point at which equilibration was judged to occur. This device was set at a sampling rate of 80 Hz, and the arterial SpO2 signal was

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averaged every 2 s. The same oximeter was used for all data collection. Subjects were excluded if the fall in SpO2 was <3%.

Other measurements included height, weight, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC ratio and the Borg score for dyspnoea on O2 and after SpO2 equilibration.

**Statistical analysis**

SpO2 versus time data for each subject were fitted to the following exponential decay model using a statistical computer program:

\[
\text{SpO2}(t) = \text{SpO2}_f + (\text{SpO2}_i - \text{SpO2}_f)(e^{-kt})
\]  

(1)

where \(\text{SpO2}(t)\) is SpO2 at a certain point in time, \(\text{SpO2}_i\) is the initial SpO2 at the time of O2 cessation, \(\text{SpO2}_f\) is the final SpO2 after equilibration breathing air and \(k\) is a time constant. This is the model used by Fildissis et al.6 with SpO2 substituted for PaO2.

The blood oxygen equilibration time was defined as the \(t_{90}\) (or \(t_{90}\)), the time taken for SpO2 to fall 90% of the difference between initial (on O2) and final (on air) values. According to an exponential decay model, true equilibration will never occur as SpO2 moves progressively closer to an asymptote. This makes it necessary to select a consistent mark to use as the definition of blood oxygen equilibration that is neither too early nor too late. The \(t_{90}\), which has been used previously, appears to fit this role6 It is given by the following equation:

\[
t_{90} = \log_{10}(\frac{k}{2.3})
\]  

(2)

The above model was fitted by maximum likelihood using the nlme package from the statistical environment R with random effects specified for \(\text{SpO2}_i\), \(\text{SpO2}_f\) and \(t_{90}\) to allow for inter-individual variation in these parameters.7

As a measure of the validity of our model, calculated \(t_{90}\) values were compared with visual estimates of SpO2 equilibration times made during data collection. A visual estimate of equilibration time was defined as the time beyond which no change in SpO2 was observed for a 2 min period. This was determined at the bedside. Potential associations between \(t_{90}\) and patient factors (including demographics, respiratory diagnosis, spirometric parameters) were explored graphically and by correlation analysis. Additional measures (such as spirometric ratio) were examined post-hoc based on feedback received during peer review.

**Results**

A total of 82 subjects (43 females, 39 males) was included. The mean age was 66 years (range: 19–87). There were 70 inpatients and 12 outpatients. The breakdown by diagnostic group is shown in Table 1. Only one patient in the COPD subgroup had a FEV1 > 50% predicted (52%).

More than half of the subjects had an estimated FiO2 of 31%, but there was a range from 24% to 50%. The SpO2 characteristics of the study population are shown in Table 2. The mean SpO2 fall after cessation of O2 was 8% and the range was from 3% to 24%. The overall mean SpO2 when breathing air was 87%, and the range was from 68% to 94%. The majority of patients had baseline SpO2 values <90%.

The distribution of \(t_{90}\) values for the whole study population is shown in Figure 1. The mean \(t_{90}\) was 8 min 18 s, with a median of 6 min 18 s, and an interquartile range of 4 min 42 s–10 min 30 s. The 95th centile value was 20 min (Table 3). When subjects with SpO2 ≥ 90% were excluded, the \(t_{90}\) distribution remained similar and the 95th centile value did not change.

Calculated \(t_{90}\) values were generally close to visual estimates of SpO2 equilibration time during data collection. A visual estimate of equilibration time was defined as the time beyond which no change in SpO2 was observed for a 2 min period. This was determined at the bedside. Potential associations between \(t_{90}\) and patient factors (including demographics, respiratory diagnosis, spirometric parameters) were explored graphically and by correlation analysis. Additional measures (such as spirometric ratio) were examined post-hoc based on feedback received during peer review.

**Table 1** Diagnostic groups

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number (% of total sample)</th>
<th>Number of males (% of group)</th>
<th>Age, mean (SD) (years)</th>
<th>FEV1 % predicted, mean (SD)</th>
<th>FEV1/FVC ratio, mean (SD)</th>
<th>FVC % predicted, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>37 (45)</td>
<td>17 (46)</td>
<td>68 (8)</td>
<td>32 (9)</td>
<td>0.44 (0.13)</td>
<td>60 (18)</td>
</tr>
<tr>
<td>Bronchiectasis (BE)</td>
<td>12 (15)</td>
<td>5 (42)</td>
<td>50 (19)</td>
<td>26 (8)</td>
<td>0.49 (0.10)</td>
<td>44 (11)</td>
</tr>
<tr>
<td>Interstitial lung disease (ILD)</td>
<td>15 (18)</td>
<td>10 (67)</td>
<td>72 (8)</td>
<td>56 (15)</td>
<td>0.74 (0.18)</td>
<td>61 (16)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (9)</td>
<td>3 (43)</td>
<td>66 (10)</td>
<td>54 (24)</td>
<td>0.71 (0.13)</td>
<td>63 (28)</td>
</tr>
<tr>
<td>Combination of respiratory diagnoses</td>
<td>11 (13)</td>
<td>4 (36)</td>
<td>67 (9)</td>
<td>51 (19)</td>
<td>0.63 (0.14)</td>
<td>68 (21)</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; SD, standard deviation.

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at least 10 min for each of these subjects. The remaining four subjects appeared to have truly prolonged t90 values (i.e. close matching of t90 and estimated SpO2). These true outliers were inpatients aged 73–79 years and comprised three subjects with COPD (FEV1 23–38% predicted) and one with ILD. Of those with COPD, only one was obese and two were known to be hypercapnic (unknown in the third). The patient with ILD had recently recovered from a pneumothorax.

**Figure 1** Distribution of t90 for whole study population. t90, time for oxygen saturation to fall 90% of difference between initial and final values.

**Figure 2** Bland–Altman plot of agreement between model-derived t90 and estimated SpO2 equilibration time. t90, time for oxygen saturation to fall 90% of difference between initial and final values.

190 was not significantly influenced by respiratory diagnosis, age, sex, FEV1 or body mass index (Fig. 3). Furthermore, magnitude of SpO2 fall, mean heart rate, haemoglobin level, FVC or known arterial partial pressure of carbon dioxide (PaCO2) > 45 mmHg were not observed to have a significant effect on t90 (data not shown). On a post-hoc analysis suggested by a reviewer, a lower spirometric ratio was significantly associated with a longer t90 (r = −0.32, P = 0.007, Fig. 3, top right).

Seventy-three subjects scored their dyspnoea on the Borg scale. Fifty-four (74%) had unchanged or improved scores off versus on supplemental oxygen. Only 12 (16%) had scores that increased by >1 after cessation of supplemental oxygen.

**Discussion**

Our results indicate that, in patients with hypoxaemia due to chronic respiratory disease, a delay of at least 20 min

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**Table 2** Oxygen saturation (SpO2) characteristics of subjects by pulse oximetry

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean initial FiO2 (%)</th>
<th>Mean initial SpO2 (%)</th>
<th>Mean SpO2 fall (%)</th>
<th>Mean SpO2 breathing air (%)</th>
<th>Proportion with SpO2 &lt; 90% breathing air</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>32.5</td>
<td>95.5</td>
<td>8.2</td>
<td>87.1</td>
<td>48/82 [59%]</td>
</tr>
<tr>
<td>COPD</td>
<td>31.3</td>
<td>95</td>
<td>7.2</td>
<td>87.7</td>
<td>20/37 [54%]</td>
</tr>
<tr>
<td>Non-COPD</td>
<td>33.6</td>
<td>95.8</td>
<td>9.5</td>
<td>87.1</td>
<td>26/39 [67%]</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>33</td>
<td>96.6</td>
<td>9.3</td>
<td>87.3</td>
<td>7/12 [58%]</td>
</tr>
<tr>
<td>ILD</td>
<td>35.9</td>
<td>96.5</td>
<td>9.7</td>
<td>86.5</td>
<td>9/15 [60%]</td>
</tr>
<tr>
<td>Other</td>
<td>34</td>
<td>93.9</td>
<td>8.4</td>
<td>85.1</td>
<td>6/7 [86%]</td>
</tr>
<tr>
<td>Combination</td>
<td>30.6</td>
<td>95.4</td>
<td>8.5</td>
<td>86.9</td>
<td>6/11 [55%]</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

**Table 3** Proportions of subjects reaching blood oxygen equilibration at progressive time points after supplemental oxygen (O2) cessation

<table>
<thead>
<tr>
<th>Time after O2 cessation (min)</th>
<th>Proportion reaching t90 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td>91</td>
</tr>
<tr>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>25</td>
<td>98</td>
</tr>
</tbody>
</table>

t90, time for oxygen saturation to fall 90% of difference between initial and final values.
after cessation of supplemental oxygen is necessary to be confident that blood oxygen equilibration has occurred. The findings of this study strengthen the foundation of evidence upon which clinical practice can be based.

Massaro et al.¹ and Sherter et al.² each demonstrated examples of longer PaO₂ equilibration times in small numbers of patients with COPD. The latter authors concluded that ABG analysis should be performed more than 25 min after stopping O₂ in this population. However, a few factors left some uncertainty over the applicability of that study’s findings to clinical practice. Firstly, the administration of 100% oxygen could potentially lead to a longer time for PaO₂ equilibration. Secondly, arterial blood samples were taken 2 min apart, so there would be a tendency to overestimate equilibration times. Thirdly, small participant numbers mean that a single outlier can have a greater impact on the conclusions drawn. In the study by Massaro et al., the stability of subjects at the time of data collection was unclear, blood was sampled at varying intervals and numbers were small.

We recognise that this study has certain limitations. While PaO₂ is the parameter of interest when assessing patients for eligibility for domiciliary oxygen, we have used a surrogate measurement, namely SpO₂. However, we feel justified in doing so as this offers superior time resolution in measuring changes in blood oxygen and greater acceptability to subjects compared with serial arterial blood sampling. Furthermore, because our primary interest was changes in blood oxygen over time rather than absolute PaO₂ values, we feel that SpO₂ is a valid measurement. The pattern of SpO₂ fall that we observed in this study describes a curve that appears the same in shape to that plotted for PaO₂ decrement in other studies.²,³,⁶

We acknowledge that there is a delay between changes in the degree of hypoxaemia and their detection by an
oximeter. Therefore, as in the aforementioned studies, this aspect of our methods is inherently weighted towards more conservative estimates of blood oxygen equilibration time. In our view, this is a preferable situation to one of underestimation.

We used a mathematical model to describe SpO₂ versus time data. In the vast majority of cases, this model appeared to be valid. The exponential decay model is biologically plausible and has been shown to describe accurately many phenomena in nature. Individually fitted exponential decay curves appeared to describe empirically observed SpO₂ data very well in almost all individuals. Furthermore, model-derived t90 values closely corresponded with human-observed equilibration times in the majority. In a few cases, however, the model did not adequately fit the data. Of seven subjects with relatively long t90 values (>15 min), this was the reason in three. This may have been due to the combination of SpO₂ variability and relatively shallow SpO₂ decay observed in these subjects.

It might be expected that the model may be less accurate when applied to subjects who had smaller falls in SpO₂ and, therefore, potentially fewer data points and greater relative variability. However, this was not observed.

We were wary that the magnitude of the SpO₂ fall could be a determinant of t90. However, no such relationship was observed. Baseline SpO₂ was also a potential factor influencing t90, and our study included subjects with a wide spread of SpO₂ values. Patients with lower SpO₂ on air were of particular interest to us because they are most relevant to supplemental oxygen prescription. The subgroup with SpO₂ < 90% was assessed separately. The 95th centile t90 for this group was identical to that for the overall study population.

Subjects did not begin the study on an equivalent FiO₂ or with the same SpO₂. The majority had an initial FiO₂ of 31%, but there were individuals for whom lower or higher FiO₂ values were more appropriate. We recognise that starting FiO₂ may influence t90, but supplemental oxygen levels were selected to simulate closely common practice.

The characteristics of the population studied must be considered in interpreting these results. Due to ease of recruitment, the majority of our subjects were inpatients at the time of data collection. Although special care was taken to ensure that these patients were as stable as possible at the time of inclusion, it cannot necessarily be assumed that their results can be generalised to an outpatient population. However, the question that this study sought to answer is most commonly relevant to an inpatient setting.

Comprehensive assessment of all the factors that may have influenced time to blood oxygen equilibration was beyond the scope of this study, although efforts were made to address some of them. Measurements of the determinants of ventilation (respiratory rate and tidal volume) were not made during the study, but presumably these factors play a part in deciding the blood oxygen equilibration time. Tachypnoea due to anxiety associated with awareness of oxygen cessation may influence t90. However, as the study conditions closely simulate the common real-life scenario in which inpatients are assessed for eligibility for home oxygen, we do not feel that this limits our conclusions. Furthermore, from a majority of subjects who scored their dyspnoea on the Borg scale, 74% had unchanged or improved scores off versus on supplemental oxygen. These findings suggest that anxiety was not a major factor influencing t90 in the majority of patients.

Comparisons between diagnostic subgroups are limited by relatively small numbers in non-COPD groups. The specific respiratory diagnosis did not appear to influence t90 significantly in this study, but further research is necessary to make definitive conclusions on this point. Full pulmonary function testing was not performed in this study, but measurements of lung volumes and gas transfer factor would be of interest. There appears to be a relationship between t90 and spirometric ratio, where a lower FEV1/FVC ratio is associated with longer t90. This makes physiological sense as greater ventilatory heterogeneity in chronic airways disease might be expected to result in longer equilibration times. Scrutiny of the characteristics of subjects with high t90 values adds support to this concept. Three of four true outliers had severe COPD. However, further study is necessary to predict more reliably which patients are most likely to have longer equilibration times.

Conclusion

Accurate baseline PaO₂ measurements can be made 20 min after cessation of supplemental oxygen in the majority of patients with chronic respiratory disease, but a longer delay is needed in some cases.
References


Prevalence of abdominal aortic aneurysm in patients referred for transthoracic echocardiography

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Key words
abdominal aortic aneurysm, echocardiography, screening, risk factor.

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Abstract

Background: Previous studies have documented the prevalence of abdominal aortic aneurysm (AAA) during transthoracic echocardiography, but the effect of such screening on subsequent vascular interventions remains unclear.

Aim: This study aimed to determine the utility of opportunistic selective screening for AAA in a contemporary large series of patients having transthoracic echocardiography.

Methods: Subjects aged 50 years or older having transthoracic echocardiography had scanning of the infrarenal aorta in a consecutive series of 10 403 men and women.

Results: The study subjects had a mean age of 70.2 ± 10.7 years, and 54.1% were men. There was a 3.5% (95% confidence interval (CI) 3.2–3.9%) prevalence of AAA with a median diameter of 39 mm (interquartile range 32 mm–48 mm). In males ≥65 years the prevalence of newly diagnosed AAA was 6.2% (95% CI 5.5–7.0%). Of those with newly diagnosed AAA, 39.7% underwent AAA repair. Age and male gender were associated with AAA prevalence. After adjustment for age and gender, echocardiographic variables associated with AAA were left ventricular end diastolic dimension (odds ratio (OR) 1.02, 95% CI 1.01–1.04), interventricular septum thickness (OR 1.11, 95% CI 1.06–1.17), left ventricular posterior wall thickness (OR 1.09, 95% CI 1.03–1.15), left atrial diameter (OR 1.04, 95% CI 1.02–1.07) and aortic root diameter (OR 1.09, 95% CI 1.06–1.11).

Conclusions: This study revealed a high prevalence of newly diagnosed AAA in a group of older men having cardiac evaluation. There was a relationship of increasing age with AAA, and a significant proportion of newly diagnosed subjects were not suitable for AAA repair.

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Introduction

An abdominal aortic aneurysm (AAA) is defined as a dilated aorta with a diameter at least 1.5 times the diameter measured at the level of the renal arteries. In most individuals, the diameter of the normal abdominal aorta is approximately 2.0 cm (range 1.4 to 3.0 cm). For practical purposes, an AAA is diagnosed when the aortic diameter exceeds 3.0 cm.\(^1,2\) Based upon available current evidence, a dimension of 5.5 cm is the best threshold for AAA endovascular or surgical repair.\(^3\)

Ruptured AAA is a major life-threatening condition with a grim prognosis. Approximately, 30% to 50% of patients with ruptured AAA die before reaching hospital. An additional 30% to 40% die after reaching the hospital without an operation. Operative mortality after rupture is 40% to 50%, making overall mortality with rupture 80% to 90%.\(^4\) In the United States, it is estimated that 9000 people die each year from a ruptured AAA,\(^5\) which corresponds to approximately 12 000 cases in Europe.\(^6\)

Ideally, AAA that are destined to rupture would be identified by screening since identification of AAA prior to rupture allows elective repair with a mortality rate of approximately 5% to 12% compared with an operative mortality of 40% to 50% after rupture.\(^7\) Ultrasound is the preferred screening mode because it is able to accurately identify AAA with sensitivity and specificity that approach 100%.\(^8,9\) Several international guidelines, recommend screening for AAA by ultrasound in high-risk populations, however, this preventive screening strategy is poorly implemented.\(^2,6,10\)

Transthoracic echocardiography (TTE) is one of the most commonly used non-invasive cardiovascular imaging methods, including visualisation of the great vessels and the abdominal aorta. Although careful examination of the abdominal aorta during TTE facilitates the diagnosis of AAA,\(^11\) examination of the infrarenal aorta is not part of the routine echocardiographic examination.

A history of smoking is considered to be the dominant risk factor for AAA.\(^12\) Ever smokers\(^13\) have an odds ratio of 3.6 compared to non-smokers for prevalence of AAA.\(^14\) There is also a strong association between smoking history and the risk of AAA-related mortality.\(^12\) The risk factors for the presence of AAA among attendees of echocardiography laboratories are similar to those reported in the general population: age, male gender, smoking, hypertension, family history of AAA and prevalent atherosclerotic diseases.\(^15\) Some echocardiography-specific parameters, such as left ventricular hypertrophy or dilation and impaired left ventricular ejection fraction, have also been reported as being associated with AAA.\(^16,17\)

Recent studies have reported a decrease in the incidence rate of AAA.\(^18-20\) As the cost effectiveness of screening programmes is affected by disease prevalence,\(^21\) we sought to evaluate a current era selective screening programme with the potential for higher detection rates of AAA than those obtained from recently conducted community-based AAA screening programmes.\(^22\) We therefore studied the prevalence of AAA in a contemporary sequential series of patients referred for transthoracic echocardiography who were screened for abdominal aortic aneurysm at the time of their echocardiogram. We also evaluated the proportion of subjects with newly diagnosed AAA who came forward to AAA repair.

Methods

Study subjects

Transthoracic echocardiogram study data on 39 176 patients (most common referral indications left ventricular function assessment or assessment of possible valvular pathology) were collected from the Nelson Marlborough District Health Board (NMDHB) Structured Query Language database from November 2005 to November 2011. NMDHB provides health services to the north of the South Island of New Zealand with an estimated population of 143 028 patients.\(^23\)

After excluding those under the age of 50 years and repeat studies on the same patients, 10 403 subjects’ echocardiographic data were included in the study. Patients under the age of 50 years were not included in the study because of their low likelihood of AAA. In subjects identified with AAA evaluation of their clinical and electronic record was undertaken to determine if the presence of AAA was previously known before their echocardiographic evaluation.

Evaluation

A full echocardiographic examination, including two-dimensional, M-mode and full Doppler evaluation was performed using Vivid 7 GE (GE Healthcare, Horten, Norway) and Vivid S6 GE (GE Healthcare, Triat Carmel, Israel) ultrasound machines, and measurements were made according to the Guidelines of the American Society of Echocardiography.\(^24,25\) Following each study, the abdominal aorta below the origin of renal arteries was scanned in the supine position in the longitudinal axis using a GE M4S ultrasound probe (1.5–3.6 MHz Matrix Array). Where visual estimation suggested an
enlarged abdominal aorta, infrarenal aortic diameter measurements were performed. Measurement of the abdominal aorta size was performed at the maximal diameter, outside to outside edge. AAA was defined as a measurement of 30 mm or greater. All measurements were performed by one echocardiographer. The measurement was entered into the database and included on the echocardiography report.

### Statistical analysis

The data were analysed using Stata (Statacorp LP, College Station, TX, USA). Continuous variables were described as mean ± standard deviation (SD) or as median and interquartile range (IQR). Independent t-test was used to compare those with and without AAA for the continuous variables. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for each risk factor. A P-value less than 0.05 was considered to be statistically significant.

### Results

The demographics of the study participants are reported in Table 1. The study subjects had a mean age of 70.2 ± 10.7 years, and 54.1% were men. In the entire study, the prevalence of AAA was 3.5% (95% CI 3.2–3.9%) with a median diameter of 39 mm (IQR 32 mm–48 mm). There were 87 subjects with AAA ≥ 50 mm, 78% of whom had a new diagnosis of AAA determined by echocardiographic screening. Of the 68 newly diagnosed subjects, 39.7% underwent AAA repair (21 subjects endovascular aortic repair, six subjects open surgical repair), 16.2% were referred for repair and assessed as either not suitable for intervention or declined intervention, and 44.1% were not referred for repair evaluation (28 subjects due to medical comorbidities, one subject returned to home country, and one subject was not referred by primary practitioner). Among the 27 subjects who underwent AAA repair, 22.2% were in the age group of 65–69 years, 55.5% were in the age group 70–79 years, 18.5% were in ≥80 age group, and only one subject was under 65 years. In the AAA size range ≥30 mm to <50 mm there were 279 subjects, with a new diagnosis of AAA in 95%. The overall prevalence of newly diagnosed AAA after echocardiographic screening was 3.2% (95% CI 2.9–3.6%) of all subjects.

Among the 366 subjects with AAA, 269 (73.5%) were males and of these, 93.7% were 65 years or older. In males 65 years or older, the prevalence of AAA ≥30 mm diameter was 6.8% (95% CI 6.0–7.7%), and the prevalence of newly diagnosed AAA was 6.2% (95% CI 5.5–7.0%). In women 65 years or older, the prevalence of AAA ≥30 mm diameter was 2.7% (95% CI 2.2–3.3%), and the prevalence of newly diagnosed AAA was 2.4% (95% CI 1.9–3.0%). The prevalence of AAA increased with age in both genders (Fig. 1). The prevalence of AAA in men aged 65–74 years was 4.7% (95% CI 3.8–5.8%), 75–84 years 8.6% (95% CI 7.2–10.2%), ≥85 years 8.9% (95% CI 6.5–11.9%). The prevalence of AAA in women increased about a decade later than in men to 3.9% (95% CI 2.9–5.0%) from the age of 75–84 years and 4.3% (95% CI 2.8–6.4%) in those ≥85 years.

The distribution of AA size according to gender is illustrated in Figure 2. In men 65 years or older, the prevalence of AAA from 50–54 mm diameter was 0.6% (24 of 3709), and the prevalence of AAA ≥55 mm was 1.1% (42 of 3709). There were only three cases of AAA ≥50 mm in men aged 50–64 years (0.2%). In women ≥50 years, the prevalence of AAA was 2.0%, and the prevalence of AAA ≥50 mm was 0.4%.

Univariate analysis showed that AAA was associated with left ventricular end diastolic dimension, left ventricular ejection fraction, left ventricular posterior wall thickness, transaortic valve peak velocity and mitral valve peak E wave velocity (Table 2). Logistic regression analysis showed that AAA was associated with increasing age and gender with odds ratios of 1.07 (95% CI 1.06–1.09) and 0.41 (95% CI 0.33–0.52) respectively (Table 3). The echocardiographic parameters that were associated with AAA, after adjusting for age and gender were left ventricular end diastolic dimension (OR 1.02, 95% CI 1.01–1.04), interventricular septum thickness (OR 1.11, 95% CI 1.06–1.17), left ventricular posterior wall thickness (OR 1.09, 95% CI 1.03–1.15), left atrial diameter (OR 1.04, 95% CI 1.03–1.05) and aortic root diameter (OR 1.09, 95% CI 1.06–1.11). There was a weak inverse relationship with left ventricular ejection fraction.

### Discussion

The findings of this study indicate that screening for AAA in men 65 years or older at the time of transthoracic echocardiography identifies, by contemporary...
standards, a high prevalence of AAA. Screening in women 65 years or older identifies a 2.5-fold lower AAA prevalence than in men, but a higher prevalence of AAA compared to a recently reported primary community AAA screening programme in 70-year-old women.

Randomised trials of AAA screening in men conducted through to the late 1990s reported AAA prevalence rates ranging from 4.0% (age range 64–73 years) in the Viborg Study to 7.6% (age range 65–80 years) in the Chichester study. However, a more contemporary Swedish screening programme performed from 2006–2009 reported AAA prevalence in men aged 65 years of only 1.7%. This lower prevalence likely reflects the screening age of 65 years, but may also relate to a reduction in the incidence of AAA. Sandiford et al. reported AAA-related mortality in New Zealand men dropping by 53% between 1991 and 2007, and Norman et al. reported a 6%/annum fall in mortality in Western Australia between 1999 and 2006. The present contemporary New Zealand echocardiographic study identified a high

Figure 1 Prevalence of abdominal aortic aneurysm (AAA).

Figure 2 Distribution of abdominal aortic aneurysm size.
prevalence of newly diagnosed AAA of 6.2% in men 65 years or older despite the reported decrease in incidence which occurred through the study period.\textsuperscript{19}

The effectiveness of AAA screening in reducing AAA related mortality has been shown in men over the age of 65 years.\textsuperscript{27–30} Cosford et al. in a Cochrane review reported no associated reduction in total mortality,\textsuperscript{31} although 13 years follow up of Multicentre Aneurysm Screening Study randomised trial of AAA showed a reduction in all-cause mortality.\textsuperscript{32} Screening for AAA in women has shown a prevalence of 1.3%, six times lower than in men with no effect on mortality from AAA rupture.\textsuperscript{33} There are concerns that the fall in disease prevalence may adversely affect the value of established screening programmes for AAA.\textsuperscript{18,19,22}

The 2014 European Society of Cardiology guidelines on the diagnosis and treatment of aortic diseases suggest a potential benefit of opportunistic screening for AAA during transthoracic echocardiography.\textsuperscript{14} On the basis of the present study findings of a 6.2% prevalence of newly diagnosed AAA in men aged 65 years and older, it is recommended that screening of the infrarenal aorta for AAA at the time of transthoracic echocardiography be further evaluated with additional studies, including randomised trials and cost-effectiveness studies. The present study shows there is a trade off between detecting a higher prevalence of AAA and greater general morbidity and mortality in the very elderly. The US Preventive Task Force recommendation is that screening be limited to men aged 65–75 years who have ever smoked\textsuperscript{35} based on the evidence that smoking is a risk factor associated with a higher prevalence of AAA in screened populations. In the present study, the yield of screening for AAA in men aged 50–64 years having transthoracic echocardiography was low at 0.9%, and the effectiveness of screening in this group is uncertain. In accordance with our findings, no recommendation for or against screening was made in men aged 50–64 years by the US Preventive Task Force.\textsuperscript{35}

An early randomised clinical trial commenced in 1989 reported an AAA prevalence of 1.3% in women aged

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Absence of AAA</th>
<th>AAA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>9729</td>
<td>357</td>
<td>53.31 ± 8.66</td>
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<tr>
<td>LV ejection fraction (%)</td>
<td>10 031</td>
<td>366</td>
<td>54.5 ± 15.48</td>
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<td>IVS (mm)</td>
<td>9673</td>
<td>350</td>
<td>12.4 ± 2.21</td>
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<tr>
<td>LVFW (mm)</td>
<td>9669</td>
<td>350</td>
<td>12.2 ± 2.26</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>9706</td>
<td>356</td>
<td>45.2 ± 7.26</td>
</tr>
<tr>
<td>AV Peak vel (m/s)</td>
<td>9790</td>
<td>365</td>
<td>1.94 ± 0.86</td>
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<tr>
<td>AV Grad max (mmHg)</td>
<td>1798</td>
<td>133</td>
<td>34.3 ± 22.17</td>
</tr>
<tr>
<td>MV E Wave (m/s)</td>
<td>9736</td>
<td>363</td>
<td>0.72 ± 0.27</td>
</tr>
<tr>
<td>A Root Dia (mm)</td>
<td>9706</td>
<td>355</td>
<td>36.6 ± 4.27</td>
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</table>

AAA, abdominal aortic aneurysm; A Root Dia, aortic root diameter; AV Grad max, maximal gradient across the aortic valve; AV Peak vel, peak velocity across aortic valve; IVS, interventricular septum thickness; LA, left atrial; LV, left ventricular; LVED, left ventricle end diastolic dimension; LVFW, left ventricular posterior wall thickness; MV E Wave, mitral valve peak E wave velocity.

### Table 3

<table>
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<tr>
<th>Characters</th>
<th>Odds ratio</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>P</th>
<th>Odds ratio&lt;sup&gt;†&lt;/sup&gt;</th>
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<th>Upper CI</th>
<th>P-value</th>
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<td>1.06</td>
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<td>–</td>
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<tr>
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<td>0.33</td>
<td>0.52</td>
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<td>1.03</td>
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<tr>
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<td>1.12</td>
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<td>1.06</td>
<td>1.11</td>
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<td>MV E</td>
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<td>0.91</td>
<td>1.97</td>
<td>0.144</td>
<td>0.80</td>
<td>0.53</td>
<td>1.21</td>
<td>0.287</td>
</tr>
</tbody>
</table>

<sup>†Adjusted for age and gender</sup>

A Root Dia, aortic root diameter; IVS, interventricular septum thickness; LA Dia, left atrial diameter; LVED, left ventricle end diastolic dimension; LVEF, left ventricular ejection fraction; LVFW, left ventricular posterior wall thickness; MV E, mitral valve peak E wave velocity.

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65–80 years with no reduction in ruptured aneurysm rate in the screened group. A subsequent large study of AAA screening conducted between 2003 and 2008 has reported an AAA prevalence of 0.4% in women aged 50 years or older, suggesting there has also been a fall in AAA prevalence in women consistent with recently published AAA mortality studies. A recent study in 70-year-old women reported a prevalence of 0.5% and concluded screening women of this age who do not smoke as futile. In the present study, we found a relatively high prevalence of AAA in women 65 years or older of 2.7% which requires confirmation in future studies. The highest prevalence was seen in the age range 75–84 years and ≥ 85 years. It remains unclear whether this prevalence is high enough for routine AAA screening after transthoracic echocardiography to lead to a reduction in AAA-related mortality in women of this age group. It is therefore concluded there is insufficient evidence at this time to recommend this type of screening in women aged 65 years or older. It may be reasonable to consider testing such a screening approach in a future randomised trial.

Visualisation of the infrarenal abdominal aorta during transthoracic echocardiography is entirely feasible, with diagnostic quality images obtained in 82–99.7% of subjects. Additional time taken to perform the examination ranges from 1.1 min to below 5 min. A potential limitation of this screening approach is that cardiac sonographers are generally not trained in vascular ultrasound. A recent prospective multicentre study addressed this by training cardiac sonographers using a video clip and collegial support with an overall 96.7% success rate in obtaining images of the infrarenal aorta.

Previous studies performed in the 1990s of ultrasound screening for AAA during transthoracic echocardiography reported AAA prevalence rates of 3% to 6% in unselected patients and 6.5% in hypertensive patients. More recent studies in unselected patients have reported lower AAA prevalence rates of approximately 1% although the mid to upper range of 3.8% to 6% appears unchanged from earlier reports. Our findings suggest that patients included in this study may have a higher prevalence of AAA largely related to their age and potentially multiple other cardiovascular comorbidities due to the selected nature of the population having transthoracic echocardiography.

Age, male gender, cigarette smoking, hypertension and presence of atherosclerotic disease have been reported to be associated with AAA in general screening studies and echocardiographic series. In this study, we did not have records of systolic blood pressure or history of hypertension available. The present study confirmed that age and male gender were associated with an increased prevalence of AAA. Independent associations with AAA were also present for; left ventricular end diastolic dimension, interventricular septum thickness, left ventricular posterior wall thickness, left atrial diameter and left ventricular ejection fraction similar to previous reports. The relationship between increased diameter of the ascending aorta and AAA may support the concept of ‘systemic arteriomegaly’ being important in the pathogenesis of AAA with focal dilation of the AAA being a manifestation of a systemic disease of the vasculature.

This study was performed using an echocardiographic database, and therefore there were limited demographic descriptors available for the study population. In particular, the smoking status of the study cohort was unknown, and therefore it was not possible to determine whether stratifying for this risk factor would further improve the yield from this type of screening. Despite this limitation, a high yield of newly diagnosed AAA was obtained in men aged 65 years and older. This suggests that patients referred for transthoracic echocardiography have a significant proportion of risk factors for AAA, such as smoking, hypertension and atherosclerotic disease as has been reported in previous echocardiographic series. While the yield of screening older men having echocardiographic studies appears high, we are unable to determine the effect at a population level of such screening. However, it is probable that only a small proportion of the Nelson community are referred for echocardiography studies, it is therefore unlikely that such a screening approach will significantly alter the overall prevalence of AAA in the community. The other limitation of this type of high-risk screening strategy is that it identifies AAA in persons with comorbidities not suitable for surgical repair.

**Conclusion**

Screening for AAA has proven to be beneficial in men aged 65 years or older by reducing mortality associated with ruptured AAA. Screening in a group of older men having cardiac evaluation revealed a high prevalence of newly diagnosed AAA, but a significant proportion of these subjects were not suitable for AAA repair. Further studies are required to evaluate the utility and cost effectiveness of this type of high-risk screening strategy.
References


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Echocardiography and abdominal aortic aneurysm

Factors relating to consent for organ donation: prospective data on potential organ donors


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Key words
brain death, circulatory death, consent, organ transplantation, prospective audit.

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Abstract

Background: Obtaining family consent to organ donation is a significant obstacle to improving further Australian deceased organ donation rates. Currently, neither the consent rates for donors eligible to donate after circulatory death, nor factors that influence decision to decline or consent to donation in general are known in Australia.

Methods: This study at four university teaching hospitals in Melbourne, Victoria, examined consecutive patients where organ donation was discussed with the family.

Results: A total of 123 cases were identified; the family consent rate was 52.8%, and 34.1% proceeded to donation. Consent to donation was related to potential donor factors such as country of birth, cultural background in Australia, a non-religious or Christian background and registration on the Australian Organ Donor Register. Family-related factors included being English speaking and having knowledge of the deceased’s wishes about organ donation. Family of donation after circulatory death-eligible donors were less likely to consent to donation than the family of donation after brain death-eligible donors, although not reaching statistical significance. Among consented potential donors, those eligible for donation after brain death and with a shorter length of stay were more likely to proceed to donating organs for transplantation.

Conclusion: Despite a small sample size, these findings describe current consent and donation rates and associated factors and may assist in improving conversations about organ donation.

Introduction

Australia has experienced a recent increase in the rate of deceased organ donations. Despite this increase, around 1500 Australians remain on organ transplantation waiting lists at any time. With 1053 organ recipients in 2012 and 1122 in 2013, the demand for organs for transplantation is perpetually unmet, resulting in people dying while on the waiting list every year.

In Australia, deceased organ donation can occur through two pathways. Traditionally, donation has occurred following brain death (donation after brain death (DBD)), but donation after circulatory death (DCD) is becoming increasingly frequent. DBD occurs following brain death and the deceased proceeds to donation with cardiorespiratory support. DCD occurs in Australia in a controlled setting, that is, following withdrawal of cardiorespiratory support (WCRS) and declaration of death occurs when the circulation ceases. Potential donors are defined as patients who are either confirmed to be or are likely to become brain dead (DBD pathway), or are thought likely to die within 90 min of WCRS (DCD pathway) and who appear medically suitable to donate organs. In Australia, the GIVE Clinical Trigger was introduced to increase the early recognition of potential donors, that is, those who were intubated and ventilated and were receiving end-of-life care. It is current Australian practice to seek consent from the next of kin, usually a family member or partner, hereafter termed family, to proceed with organ donation even if the person who has died has registered consent to donate on the Australian Organ Donor Register (AODR). Discussing donation with families and obtaining consent does not follow a standard protocol or path and will differ depending on the circumstances. Ideally, conversations occur in the intensive care unit. Most commonly, organ donation conversations for
Factors relating to consent for donation

The family’s knowledge of the potential donor’s wish to donate organs is strongly associated with consent. However, due to the absence of Australian data about factors that influence consent, public awareness campaigns promoting discussion of donation are currently informed by mostly North American and Spanish studies. It is important to know which factors affect consent decisions in the Australian setting so that these public awareness and education campaigns, as well as healthcare staff training and organ donation request models, can be designed specifically for the Australian context.

This study, which is part of a larger mixed methods study, aimed to identify the factors associated with family consent or non-consent for organ donation. To our knowledge, this is the first study in Australia to assess factors associated with consent decisions that include both consenting and non-consenting family.

Methods

Data collection

Prospective data on deceased donors and potential donors were collected from four sites between April 2012 and September 2013 with varying starting dates due to human research ethics committee (HREC) constraints. The primary purpose was to detect cases for interview in qualitative research on factors affecting the decision to donate organs. This enabled data from the whole pool of prospective consecutive potential donors to be gathered and analysed for the current study. At each site, a nurse or medical donation specialist (DS) collected and reviewed data of deceased patients to identify (potential) organ or tissue donors for the OTA’s audit. The DS at the four participating sites collected similar health, demographic and other additional relevant characteristics about potential organ donors from the hospital database, typed notes in the medical file, hospital clerical data or directly from the treating clinician. A subsample of participants was subsequently invited for a qualitative interview; these results will be reported elsewhere. Approval from the HREC committees at the participating hospitals was obtained.

Instruments

The data collection tool was based on existing literature and further amended and developed by the research team including psychologists, researchers, four DS employed by the OTA and a Family Support Coordinator. In consultation with the relevant HREC, the tool was further amended. The data collection tool consisted of a password-protected document where research staff could...
Table 1 Donor categories and definitions

<table>
<thead>
<tr>
<th>Donor category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential donor</td>
<td>Patient who is medically suitable to donate organs and has the potential to do so either through donation after brain death (DBD) or donation after circulatory death (DCD).</td>
</tr>
<tr>
<td>Actual organ donor</td>
<td>Deceased (. . .) person from whom at least one solid organ or part of it has been recovered for the purpose of transplantation.</td>
</tr>
<tr>
<td>Intended donor</td>
<td>A person for whom the donation workup was initiated (. . .) but donation did not proceed.</td>
</tr>
<tr>
<td>Planned DCD donor†</td>
<td>A patient who was consented for DCD organ donation, irrespective of whether withdrawal of cardiorespiratory support or organ donation actually occurred.</td>
</tr>
<tr>
<td>Non-consent donor‡</td>
<td>The family declined organ donation or the family was not approached because it was known that the patient was opposed to organ donation, such as a documented refusal on the AODR.</td>
</tr>
</tbody>
</table>

†If a planned DCD donor also fitted the ‘Actual organ donor’ category, they were only classified in the latter category. This study did not include missed or unrealised potential donors where the family was not approached and organ donation was not considered. AODR, Australian Organ Donor Register.

complete the following data items from the hospitals’ information systems, the data collected for the OTA’s audit, as well as from interviews that were held in a subsample: date of birth; admitting hospital; date and time of hospital admission; date and time of death; gender; country of birth (COB); cultural background; religion; presenting complaint; location where potential donor status was identified; potential donation pathway (DCD or DBD); AODR status; outcome of potential donation; and whether the patient’s family required a translator, whether they were aware of the patient’s donation wish and whether they provided consent. Due to the varying origin of these data, there were no predetermined categories for variables such as cultural background or religion.

Participants

Data were collected on all potential donors who were considered medically suitable for organ donation at the time organ donation was discussed with the family, regardless of the outcome of the consent conversation or the donation. Participants were categorised according to definitions derived from the OTA audit13 and World Health Organization14 (Table 1).

Data analysis

Data were exported to SPSS 22.0 (SPSS, Chicago, IL, USA) and characteristics of potential donors were compared for two outcome measures: (i) family consent; and (ii) whether those for whom consent was obtained proceeded to organ retrieval. We used independent samples median test for continuous variables without a normal distribution, and Chi-squared or Fisher’s exact tests for categorical variables. Chi-squared results were only interpreted if there was an expected count of 5 in 280% of cells. For all inferential analyses, alpha was set at 0.05 and two-tailed tests of significance were used.

Sample size

This study recruited 100% of potential donors where family was consulted from participating hospitals during the study period. Sample size was determined by the desire to interview a subsample of cases meeting more stringent inclusion criteria (e.g. English speaking) in both the consent and non-consent arms of the associated qualitative study until saturation of themes was reached. This occurred when data on 123 potential organ donors were collected and recruitment was halted. Based on the sample obtained, post-hoc analysis revealed that there was sufficient power to detect differences in proportions for dichotomous variables that varied between 15% and 27%, depending on the proportion, when alpha was set at 0.05, with 80% power, and two-tailed tests were used.

Results

In total, 123 consecutive potential organ donors were identified for inclusion in the study, including 42 organ donors, 12 intended donors, 11 planned DCD donors and 58 non-consent potential donors (whose families declined consent for donation). The consent rate was 52.8% (65/123), and the conversion rate was 34.1% (42/123). The 42 organ donors, including 14 (33%) DCD donors, donated 65 kidneys, 27 livers (one for research), 22 pairs of lungs, 10 hearts (three of which were used for research and one was not used as there was no suitable recipient) and 5 pancreases. There were 124 solid organs transplanted, average 3.0 per donor, and all donors had one or more organs transplanted. In addition, 10 organ donors also donated tissues including eye, bone and/or skin tissues; and of those not able to donate solid organs, seven donated eyes or corneas. The median age at death was 58.5 years (46.8-67.6) and the median time between hospital admission and death was 66.0 h (28.4-120.0). Further demographic data are depicted in Table 2.

The data included in the category ‘not recorded’ were excluded from further bivariate analysis. Variables significantly related to consent were hospital, COB and cultural background (collapsed into three groups for the purpose of analyses). Families of potential donors from Australia...
Table 2 Demographic and donation-related data of potential organ donors

<table>
<thead>
<tr>
<th></th>
<th>Whole sample</th>
<th>Consent for organ donation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
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</tr>
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<tr>
<td>Hospital 2</td>
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</tr>
<tr>
<td>Hospital 3</td>
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<td>Hospital 4</td>
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<td><strong>Gender</strong></td>
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</tr>
<tr>
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</tr>
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<td></td>
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<tr>
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<tr>
<td>United Kingdom</td>
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<td></td>
</tr>
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<tr>
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<tr>
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<td>2.4</td>
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<td></td>
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<td>61.8</td>
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<tr>
<td>DBD</td>
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<td>Cerebrovascular</td>
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<td>52.8</td>
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<td>Trauma</td>
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<td>30.1</td>
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<tr>
<td>Other</td>
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<td>8.1</td>
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<td><strong>Location where potential donor status identified</strong></td>
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<td></td>
</tr>
<tr>
<td>ICU</td>
<td>105</td>
<td>85.4</td>
</tr>
<tr>
<td>ED</td>
<td>17</td>
<td>13.8</td>
</tr>
<tr>
<td><strong>Family speaks English</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No or very limited</td>
<td>16</td>
<td>13.0</td>
</tr>
<tr>
<td>Yes</td>
<td>107</td>
<td>87.0</td>
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<td><strong>Australian Organ Donor Register record</strong></td>
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<tr>
<td>Yes (all consent)</td>
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<td>8.9</td>
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<tr>
<td>Not registered on AODR</td>
<td>87</td>
<td>70.7</td>
</tr>
<tr>
<td>Not checked in recorded</td>
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<td>20.3</td>
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<tr>
<td><strong>Family aware of patient’s wish</strong></td>
<td></td>
<td></td>
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<td>No</td>
<td>47</td>
<td>38.2</td>
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<td>58</td>
<td>47.2</td>
</tr>
<tr>
<td>Not recorded</td>
<td>18</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Percentages are adjusted for missing data. AODR, Australian Organ Donor Register; DBD, donation after brain death; DCD, donation after circulatory death; ED, emergency department; ICU, intensive care unit.
and New Zealand were more likely to consent to donation, whereas families of those born in Asia, Melanesia and Polynesia were less likely to consent. Data relating to religion (collapsed into four groups) showed that family of potential donors who affiliated with a religion other than Christian were less likely to consent. Other factors significantly related to consent were whether the family spoke English (considered non-English speaking if requiring a translator); whether the family were aware of the patient’s wish regarding donation; and whether the patient was registered on the AODR (Table 3). Although not statistically significant, donation pathway showed a trend with families of those eligible for the DBD pathway more likely to consent compared with those eligible for DCD pathway. Age, time spent in hospital, gender, presenting complaint and location where the potential donor was identified were not significantly related to consent (results not shown). Overall, potential DBD donors spent more time in hospital compared with potential DCD donors (medians of 80.5 h vs 42.7 h; \( P = 0.012 \)) and were more likely to proceed to donation compared with potential DCD donors (59.6% vs 18.4%; \( P < 0.001 \)).

Additional analyses on those for whom consent was obtained \( (n = 65) \) showed that none of the above factors was significantly related to proceeding to organ retrieval, except for donation pathway (DCD 40% vs DBD 93.3%, \( P < 0.001 \)) and time spent in hospital; those who proceeded to donation spent a median of 46.9 h in hospital, whereas those not proceeding to donate spent a median of 138.9 h in hospital \( (P = 0.007) \).

### Discussion

This is the first study to report demographic and donation-related data of potential organ donors and to draw comparisons between consenting and non-consenting family in Australia.

The consent rate of 53% in this study was lower than the national consent rate of 61% (2012 and 2013) published by the OTA.\(^1\)\(^3\) This difference may be due to variations in patient cohorts. This study included all potential donors including those with confirmed or suspected brain death and imminent brain death (those who were thought likely to progress to brain death had physiological supports been maintained) as well as potential DCD donors. The annual performance report published by OTA included potential donors with confirmed or suspected brain death, but does not report on potential

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<table>
<thead>
<tr>
<th>Hospital</th>
<th>Consent</th>
<th>Non-consent</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11 52.4</td>
<td>10 47.6</td>
<td>( P = 0.043 )</td>
</tr>
<tr>
<td>2†</td>
<td>20 40.0</td>
<td>30 60.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9 52.9</td>
<td>8 47.1</td>
<td></td>
</tr>
<tr>
<td>4‡</td>
<td>25 71.4</td>
<td>10 28.6</td>
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</table>

<table>
<thead>
<tr>
<th>Country of birth</th>
<th>Consent</th>
<th>Non-consent</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia or New Zealand‡</td>
<td>49 65.3</td>
<td>26 34.7</td>
<td>( P &lt; 0.001 )</td>
</tr>
<tr>
<td>Europe</td>
<td>14 45.2</td>
<td>17 54.8</td>
<td></td>
</tr>
<tr>
<td>Asia, Melanesia and Polynesia†</td>
<td>1 6.7</td>
<td>14 93.3</td>
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<table>
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<th>Consent</th>
<th>Non-consent</th>
<th>( P )-value</th>
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<tr>
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<td>42 73.7</td>
<td>15 26.3</td>
<td>( P &lt; 0.001 )</td>
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<td>Europe</td>
<td>18 41.9</td>
<td>13 58.1</td>
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<tr>
<td>Asia, Melanesia and Polynesia†</td>
<td>1 5.0</td>
<td>19 95.0</td>
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<th>Consent</th>
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<th>( P )-value</th>
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<tr>
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<td>27 62.8</td>
<td>16 37.2</td>
<td>( P = 0.011 )</td>
</tr>
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<td>Christian other than Catholic</td>
<td>20 69.0</td>
<td>9 31.0</td>
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<td>Other religions†</td>
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<th>Consent</th>
<th>Non-consent</th>
<th>( P )-value</th>
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<tbody>
<tr>
<td>DCD</td>
<td>35 46.1</td>
<td>41 53.9</td>
<td>( P = 0.065 )</td>
</tr>
<tr>
<td>DBD</td>
<td>30 63.8</td>
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<table>
<thead>
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<th>Consent</th>
<th>Non-consent</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None or limited†</td>
<td>2 12.5</td>
<td>14 87.5</td>
<td>( P = 0.001 )</td>
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<tr>
<td>Yes‡</td>
<td>63 58.9</td>
<td>44 41.1</td>
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</table>

<table>
<thead>
<tr>
<th>Family aware of patient’s wish</th>
<th>Consent</th>
<th>Non-consent</th>
<th>( P )-value</th>
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</thead>
<tbody>
<tr>
<td>No†</td>
<td>16 34.0</td>
<td>31 66.0</td>
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</tr>
<tr>
<td>Yes‡</td>
<td>41 70.7</td>
<td>17 29.3</td>
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</table>

<table>
<thead>
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<th>Consent</th>
<th>Non-consent</th>
<th>( P )-value</th>
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<tbody>
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</tr>
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<td>11 100.0</td>
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</tr>
<tr>
<td>Unknown/not checked†</td>
<td>5 20.0</td>
<td>20 80.0</td>
<td></td>
</tr>
</tbody>
</table>

†Significantly less often in the consenting group. ‡Significantly more often in the consenting group §Not statistically significant (= 0.065). DBD = donation after brain death; DCD = donation after circulatory death.
Factors relating to consent for donation

donors with imminent brain death, or potential DCD donors who are thought to have lower conversion rates.

To determine consent rates, the current study included all potential DCD and DBD donors considered medically suitable for donation at the time of the family’s decision, even if they were later considered medically unsuitable. Including potential DCD donors in consent rate calculations resembles the way family consent rate is defined and calculated in some other countries; however, imminent or unconfirmed brain dead potential donors are not included universally when reporting consent rates, and practices regarding brain death testing differ between countries.15,16 Recently, there have been some calls for a standard method of assessing the potential donor pool and consent rates; however, these have not yet been adopted.17,18 As the OTA does not report consent rates of potential DCD donors, these rates are not well known in Australia.

The conversion rate of 34% (18% for DCD and 60% for DBD) was also lower than OTA targets. Slightly higher than reported conversion rates of 54% and 45% in 2012 and 2013,1 the conversion rate for potential DBD donors was 60%. This is again likely due to different patient inclusion, as this study did not include missed potential donors. National data on missed potential donors varied between 3% and 10% in 2012 and 2013;1,3 the conversion rate, therefore, could have been lower if missed potential donors had been included in this study. The conversion rate for potential DCD donors was much lower at 18%, similar to other countries.13 This may reflect the complexities of the DCD donation process, limited time frames for organ retrieval and difficulties in predicting outcomes. Also, as DCD pathways in some of the hospitals involved were introduced very recently, not all staff may have been fully familiar with the protocols.

Knowledge of the wishes of the deceased was highly related to consent in our study. This finding is consistent with US literature, which identifies such knowledge as one of the main predictors for family consent.9,11,12,19 Promoting family conversation about donation and knowing a loved one’s wishes are key components of the OTA’s public awareness campaign and would seem, in the Australian context, to be of great relevance. Family were aware of the deceased’s wish regarding organ donation in less than 50% of cases in our study, consistent with OTA’s own research.6

Registration on the AODR is also highly related to consent, again consistent with the US literature. National data are unavailable, but a recent Victorian audit reported that the AODR was only checked in 50% of cases,20 which contrasts with the 80% found in our study, although in both studies, it is not known whether the AODR was checked before consent was requested. If the AODR is not checked before the conversation with the family, it is regular practice to check the AODR for potential donors for whom verbal consent has been obtained, but not those for whom consent was refused, which may explain the association between consent and checking the AODR.20 In both samples, around 10% of potential donors were registered, whereas it is estimated that around a third of the population over 16 years of age is now registered on the AODR.21

Among non-English-speaking family, the consent rate was very low at 12.5%. This has significance for those having consent conversations with families from non-English-speaking backgrounds and for those providing education in the sector. Discussions about organ donation are often very sensitive given the circumstances and require explanations of complex medical issues. Verbal and non-verbal communication including perceived compassion, sensitivity and care provided to the patient and family are factors known to influence donation decisions,19,22,23 and communication is more challenging across language and cultural barriers.24 Our own experience suggests that barriers to clear communication with non-English-speaking family include the (after-hours) availability of interpreters to participate in often lengthy discussions, continuity of care, and trust by both the family and the clinician in the interpreter. However challenging, it is vital that these families are provided with the opportunity to be fully informed of the opportunity to donate their organs.25

The significant association of COB with consent rate, with family of potential donors born in Australia or New Zealand more likely to consent compared with those born in Asia, confirms findings in US and UK studies that the minority groups are less likely to consent.10,26 Although the numbers in the religion subgroups were small, it is noteworthy that the consent rate was lower among those of religious backgrounds other than Christian, consistent with existing literature showing minorities are less likely to consent.27 For this variable, we largely relied on data collected by hospital clerical staff and were not able to assess for strength of religious beliefs, but this has been shown to influence willingness to donate among the general public,27 and future studies may be able to assess this further. The variables COB, cultural background, religion and whether the family spoke English are likely inter-related, and it is therefore difficult to distinguish which has the strongest predictive value, as some of the groups in our sample were small. Recent improvements to the methods and tools used to collect national data by the OTA may lead to a database with a larger sample size so that analyses may elucidate this further.

There was a significant difference in consent rate between hospitals, and further research is needed to
assess whether request models may explain these differences. Of note, 13.8% of all potential donors were identified and referred from ED indicating that this is an important site for donor recognition and referral.28 There was a trend for families of those patients eligible for the DBD pathway to be more likely to consent to donation, and proceed to organ retrieval, in line with data from the UK. The reasons for this may be hypothesised to include the increased certainty associated with brain death determination and the knowledge that following consent, donation is more likely to proceed in DBD; however, there is currently a lack of literature regarding this.

Among the subgroup for whom consent was obtained, those potential donors proceeding to donation had spent less time in hospital between admission and death compared with those not proceeding to donation. This may be due to a proportion of planned DCD patients who did not die in the timeframe required for donation to proceed and therefore had a longer length of stay; however, length of stay could also be associated with a range of other variables such as the underlying illness or treatment plan. A US study has previously indicated that longer length of stay increases the likelihood of medical complications prohibiting donation.24 However, further research needs to be undertaken to assess this in the Australian setting.

Age, time spent in hospital, gender, presenting complaint and location (ED or ICU) where the patient was identified as a potential donor were not significantly related to consent. Some of these factors have previously been shown to affect consent or conversion rates. However, our sample size is small and may have been underpowered to detect smaller differences between groups. In an attempt to verify that our sample was similar to the national sample, a comparison was made of demographic characteristics between the organ donors in our study and organ donors nationally recorded in the annual Australian and New Zealand Organ Donation Registry (ANZOD) 2012 Report.29 Our sample was older overall and included more non-religious donors (not taking into account the 50% in the unknown category in the ANZOD report), but in terms of gender and COB, it was largely comparable. National data regarding potential donors not proceeding to donation are not available. Our sample represented potential organ donors mostly from Victoria, including from rural areas, who died in inner-city hospitals in Melbourne, which may reduce the generalisability but does not negate the importance of these results.

Conclusion

Our data have the potential to shed further light on the factors influencing consent. This should guide further research into consent and non-consent to organ donation among families of potential donors in Australia and further inform health professionals responsible for donation-related processes and conversations with families and those involved in community education, potentially improving consent rates.

Acknowledgements

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Clinical outcomes of chronic hepatitis C patients related to baseline liver fibrosis stage: a hospital-based linkage study

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Key words
liver fibrosis, liver-related death, decompensation, hepatocellular carcinoma, hepatitis C.

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Abstract

Background and Aims: Rates of long-term clinical outcomes of chronic hepatitis C in patients with none, mild or severe liver fibrosis are required to determine benefits of anti-viral therapies. This study evaluated long-term outcomes for chronic hepatitis C stratified by all Metavir fibrosis stages.

Methods: Clinical outcomes were determined using population-based data linkage methodology for 880 hepatitis C patients who had a liver biopsy performed from 1992 to 2012.

Results: During 9386 person-years of follow up, 28 patients developed hepatocellular carcinoma, 58 developed liver decompensation and 122 died or underwent liver transplantation. There was no significant difference in liver-related death for those with F0–F2 with an 18-year survival probability >94%. Hazard ratio of liver-related death for F3 compared with F0–F2 was 4.24 (P = 0.003), with no significant difference in the first 13-year follow up. The 15-year decompensation-free survival for F0, F1 and F2 was 100%, 96% and 94% respectively and for hepatocellular carcinoma-free survival was 100%, 99% and 98%. Hazard ratio of liver complication (hepatocellular carcinoma or decompensation)-free survival for F3 compared with F0–F2 was 3.22 (P = 0.001), with no significant difference during the first 7-year follow up. F4 had significantly higher risk of liver-related death, decompensation and hepatocellular carcinoma than F3 (P < 0.001).

Conclusions: Chronic hepatitis C patients with F2 or less had few liver complications after 15 years. For F3 patients, the significant increase in liver-related death occurred after 13 years and for liver complications after 7 years.

Introduction

Hepatitis C virus (HCV) infection affects about 180 million people worldwide and predisposes these individuals to complications of cirrhosis and death.1 Patients with chronic hepatitis C (CHC) after 5–7 years of follow up had a three times higher risk of overall death and a 17 times higher risk of liver-related death than the general population.2,3 Descriptions of the natural history of HCV infection vary greatly and this in part is due to constraints of study design as a consequence of the uncertain time of acquisition of infection and the prolonged course of disease. Nevertheless, several well-documented host-related factors including age, gender, race and alcohol consumption influence the progression of CHC and add to the variability of individual disease progression rates.4–6 Viral factors are mostly associated with treatment outcomes rather than progression of CHC.4 The risk of liver-related morbidity and mortality was minimal in the first two decades after acquisition of HCV infection but divergent results were found beyond this time. After 25-year follow up, the rate of hepatocellular carcinoma (HCC) development and liver-related death in young German women infected with HCV following anti-D globulin use was 1.5% and 0.5% respectively.7 Another study after 31-year follow up reported worse outcomes with HCC development in 4.7% and liver-related death in 5.3%.8
In clinical practice, the vast majority of CHC patients present after an unknown time of infection so that the severity of liver disease may potentially vary from none to severe. Therefore, liver biopsy and more recently non-invasive markers of liver fibrosis have been used to determine the severity of liver fibrosis at a given time point and allow prediction of the risk of liver-related adverse outcomes and determine the timing of treatment. The rate of adverse clinical outcomes is well described for those HCV patients with severe fibrosis, but data are lacking for those with less severe liver fibrosis.

The aim of this study was to determine the long-term clinical outcome of CHC patients with all stages of liver fibrosis using the linked data from the Western Australia Department of Health. The Western Australia Data Linkage Unit is a validated population-based data linkage system that links multiple health-related datasets including cancer registrations, inpatient hospital morbidity and mortality records dating back to 1982, 1970 and 1969 respectively. The Hospital Morbidity Data System has 100% coverage of data for all hospital admissions in Western Australia and has been widely used in cohort and population-based studies. This study will provide important new information that will better guide individual and population-based studies.

**Methods**

One thousand and thirty-three CHC patients who had a liver biopsy performed in Sir Charles Gairdner Hospital from 1992 to 2012 were included. Exclusion criteria were co-infection with hepatitis B virus or human immunodeficiency virus, liver transplantation, haemochromatosis, α1-antitrypsin deficiency, Wilson disease and autoimmune liver diseases. One hundred and fifty-three patients who had successful antiviral treatment for HCV were excluded. Patients were followed from the time of baseline liver biopsy until each clinical outcome (death, liver decompensation or HCC) or the end of study. The study was approved by the Sir Charles Gairdner Hospital Human Research Ethics Committee and the Department of Health WA Human Research Ethics Committee.

**Liver fibrosis evaluation**

Liver biopsy reports were obtained from the database of the Department of Hepatology, Sir Charles Gairdner Hospital. The severity of liver fibrosis was reported by the Department of Hepatology, Sir Charles Gairdner Hospital (Fig. 1, Table 1). Ishak stage was converted to Metavir stage according to the following scheme: Ishak 0 to F0, Ishak 1, 2 to F1, Ishak 3 to F2, Ishak 4 to F3, Ishak 5, 6 to F4. Biopsy reports before 1999 were reviewed by a specialist liver pathologist and were staged using the Metavir system.

**Outcome measures**

The Western Australia Data Linkage Unit linked 1033 patients who had a liver biopsy at Sir Charles Gairdner Hospital to the statewide hospital morbidity data system, mortality records and cancer register database. Data were extracted for each patient and included date and diagnosis of each hospital admission, date and cause of death and date of HCC diagnosis. The hospital admission diagnosis and the cause of death were recorded using International Classification of Diseases (ICD) 9 (before 1997) and ICD 10 (after 1997) classification codes.

The primary outcome was death or liver transplantation. The cause of death was categorised into liver-related death, behaviour-related death and other causes. Liver-related death was defined as: death directly attributed to liver failure, variceal bleeding, hepatorenal syndrome or HCC; death in which liver disease was a major contributing factor; or liver transplantation. Behaviour-related death was defined as death due to drug or alcohol use, drug overdose, drug or alcohol dependence and intentional self-harm. The secondary outcomes were the first episode of liver decompensation or the diagnosis of HCC. Liver decompensation was defined as ascites, hepatic encephalopathy, variceal bleeding, hepatorenal syndrome, jaundice and spontaneous bacterial peritonitis (R18, K72, I85.0, I98.3, K76.7, K65.9, R17 in ICD code 10 and 789.5, 070.44, 070.41, 456.0, 572.4, 567.23, 782.4 in ICD code 9). Patients with no evidence of decompensation 1 year prior to biopsy were considered compensated at baseline.

**Statistical methods**

Correlations were determined using the Spearman correlation coefficient. Survival was assessed using Kaplan–Meier curves and log-rank test. Cox regression was used to identify predictors of survival. The proportional hazards assumption was tested based on Schoenfeld residuals. The incidence rate was calculated as the number of events divided by at-risk person time. Two-sided P values <0.05 were considered significant.

**Results**

Of the 880 CHC patients who were included in the analysis, 833 were compensated at baseline (Fig. 1, Table 1). Sixty-eight per cent were male and the mean age was 40 years. Follow up totalled 9386 person-years with a mean of 11 years (range, 1–20). One hundred and
seventy-three patients had F0 (no fibrosis), 383 had F1, 124 had F2, 80 had F3 and 73 had F4 fibrosis. Fibrosis stage was significantly associated with age ($r = 0.38, \ P < 0.001$). During follow up, 122 died or underwent liver transplantation, 28 developed HCC and 58 developed liver decompensation. The mean age at time of death or liver transplantation was 52 years (range, 26–87), at time of HCC diagnosis was 61 years (range, 47–80) and at time of hepatic decompensation was 57 years (range, 39–84). At baseline, 15 patients had hepatic decompensation, 20 had HCC, 12 had both decompensation and HCC and these patients were followed separately (Fig. 1).

Behaviour-related death accounted for 20% of deaths. Younger age but not fibrosis stage or gender was significantly associated with higher risk of behaviour-related death with hazard ratio (HR) of 0.91 (95% confidence interval (CI), 0.86–0.96). Liver-related death accounted for 39% of deaths and 31% of these were due to HCC. Age but not gender was significantly associated with liver-related survival (HR 1.09; 95% CI, 1.06–1.11). There was no significant difference in liver-related survival between those with F0, F1 or F2 fibrosis ($P = 0.163$) with an 18-year survival probability of 99% (95% CI, 96%–100%), 96% (95% CI, 91%–98%) and 94% (95% CI, 83%–98%) respectively (Fig. 2, Table S1). The liver-related survival probability for F3 patients was 96% (95% CI, 88%–99%) at 13 years but decreased to 77% (95% CI, 51%–91%) at 18 years. Age-adjusted HR of liver-related death for F3 compared with F0–F2 was 4.24 (Table 2), with no significant difference in the first 13-year follow up. Those with F4 had significantly worse liver-related survival than F3 ($P < 0.001$) with a 5, 10 and

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline fibrosis status</th>
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<tr>
<td></td>
<td>F0</td>
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<tr>
<td>Number (%)</td>
<td>173 (21)</td>
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<tr>
<td>Mean age (SD)</td>
<td>36 (8)</td>
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<tr>
<td>Male, n (%)</td>
<td>110 (64)</td>
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<tr>
<td>Female, n (%)</td>
<td>63 (36)</td>
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<tr>
<td>Mean follow-up years (SD)</td>
<td>12.0 (4.6)</td>
</tr>
<tr>
<td>HCC, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decompensation, n (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total deaths, n (%)</td>
<td>11 (6.4)</td>
</tr>
<tr>
<td>a. Liver related, n (%)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>b. Behaviour related, n (%)</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>c. Other causes, n (%)</td>
<td>5 (2.9)</td>
</tr>
</tbody>
</table>

Figure 1 Flow chart of patient inclusion and follow up.

Figure 2 Liver-related survival for compensated patients with each Metavir stage. Metavir = 0; ———, Metavir = 1; ——, Metavir = 2; ——, Metavir = 3; —, Metavir = 4.
15-year liver-related survival probability of 83% (95% CI, 72%–90%), 57% (95% CI, 43%–70%) and 40% (95% CI, 23%–57%) respectively and the incidence rate of liver-related death was 0.051 case/person-year.

Patients with F0, F1 and F2 had excellent HCC-free survival with 15-year survival probability of 100%, 99% (95% CI, 98–100%) and 98% (95% CI, 92–100%) respectively (Fig. 3, Table S2). The 15-year decompensation-free survival for F0, F1 and F2 patients was 100%, 96% (95% CI, 93–98%) and 94% (95% CI, 86–97%) respectively (Fig. 3, Table S3). F3 patients compared with those with F0–F2 had a significantly reduced decompensation-free survival ($P = 0.009$) and HCC-free survival ($P < 0.001$). CHC patients with F3 fibrosis had a 7-year decompensation-free survival of 97% (95% CI, 89–99%) and 7-year HCC-free survival of 98% (95% CI, 90–100%), but this decreased to 86% (95% CI, 70–94%) and 78% (95% CI, 62–88%) respectively at 18 years. The age-adjusted HR for liver complications (HCC or liver decompensation)-free survival for F3 compared with F0–F2 was 3.32 (95% CI, 1.59–6.89); however, there was no significant difference during the first 7-year follow up (Table 2). F4 patients had a 5- and 10-year decompensation-free survival of 76% (95% CI, 0.63–0.84) and 58% (95% CI, 44–70%) respectively and HCC-free survival of 94% (95% CI, 84–98%) and 78% (95% CI, 62–88%) respectively. The age-adjusted HR for liver complication-free survival for F4 patients compared with those with F0–F2 fibrosis was 17.2 (95% CI, 9.34–31.5). In F4 patients, the incidence rate for liver decompensation was 0.068 cases/person-year, for HCC was 0.028 cases/person-year and for liver complications was 0.083 case/person-year.

Eighty-five patients with liver decompensation and 60 patients with HCC were identified either at baseline or during follow up and were followed for a mean of 2 years. Fifty-five decompensated patients and 30 HCC patients had a liver-related death with an incidence rate of 0.27 cases/person-year and 0.23 cases/person-year respectively. The 1-year survival probability for

<table>
<thead>
<tr>
<th>Table 2 Hazard ratio for liver complication and liver-related death</th>
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<tr>
<td>Metavir stage</td>
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<td>----------------</td>
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<tr>
<td></td>
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<tr>
<td>F0–F2</td>
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<tr>
<td>F3</td>
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<td>F4</td>
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†Hazard ratio was adjusted for age.
liver-related death in decompensated patients was 52% similar to 63% in HCC patients (Fig. 4).

**Discussion**

This study has comprehensively evaluated the long-term clinical sequelae of CHC patients stratified by all liver fibrosis stages (F0–F4). The strengths of this present study were the large well-defined cohort that included patients with all stages of liver fibrosis, particularly those with none or minimal fibrosis. The long follow up for up to 20 years and the availability of detailed outcomes for each patient have allowed a more precise analysis of the disease burden for CHC patients.

Two previous studies have reported mortality rates related to fibrosis stage for CHC patients. One studied 1050 patients, 93% of whom had Ishak stage 3 to 6, for a maximum of 6 years and found a significant increase in liver complications and mortality in those with cirrhosis compared with those without. The other study included 131 patients with Ishak stage 4 to 6 with a median follow up of 51 months and found no influence of fibrosis stage on liver-related survival. Others tested the ability of serum fibrosis markers and liver biopsy stage to predict outcomes for hepatitis C patients, but these were limited by inclusion of non-CHC patients or a limited 5-year follow-up time.

This study found that CHC patients with no fibrosis, F1 or F2 fibrosis rarely developed progressive disease and they had a minimal risk of developing liver-related morbidity and mortality during the following 15 years. The 15-year accumulative HCC-free survival, decompensation-free survival and liver-related survival probability for F2 patients was 98%, 94% and 94% respectively. The implication of these findings is that the use of expensive anti-viral treatments that have significant and severe side-effects may not be justified in those patients with F0, F1 or F2 fibrosis. Present international guidelines vary in their recommendations regarding HCV treatment based on fibrosis stage. America Association for the Study of Liver Diseases and the European Association for the Study of the Liver guidelines recommend that all patients with F2 fibrosis be strongly considered for or be treated with anti-viral medications, while Asian Pacific Association for the Study of the Liver guidelines recommend that genotype 3 patients with any stage of fibrosis be treated and those with genotype 1 be treated if they have moderate or severe fibrosis. The Australian Pharmaceutical Benefits Scheme guidelines allow federally funded subsidised treatment for CHC patients with any fibrosis stage. Clearly, these guidelines may need to be reassessed in light of the findings of this present study.

Another important finding was the delayed but significant increase in liver complications in those CHC patients with F3 fibrosis compared with F0, F1 or F2. The increased rate of liver decompensation and HCC development occurred after a delay of 7-year follow up and the increased rate of liver-related death occurred after 13 year follow up. Previous studies have found that fibrosis progression in CHC does not proceed in a linear manner and that the time needed to progress to cirrhosis from each fibrosis stage was uncertain. Based on the findings in this study that liver complications were minimal during 15 years of follow up for F2 patients and occurred after a delay of 7-year follow up for F3 patients, it could be assumed that it would take about 7 years for F3
patients and more than 15 years for F2 patients to progress to cirrhosis. The use of a repeat liver biopsy or a non-invasive marker of liver fibrosis to monitor for fibrosis progression would be useful in this situation. Surveillance for HCC and oesophageal varices may also need to be extended to those CHC patients with F3 after a follow-up period of 7 years.

The natural history of compensated cirrhotic (F4) CHC patients has been more clearly defined. A recent review summarised 13 studies and reported the range of incidence rates (cases/person-year) for the development of HCC was 0.018–0.071, for liver complications was 0.028–0.117 and for death or liver transplantation was 0.027–0.067. The results from the Western Australian CHC population in this study fall within these ranges with the corresponding incident rates of 0.028, 0.083 and 0.051 respectively. As expected, CHC patients with decompensated liver disease or HCC had significantly worse outcomes than compensated cirrhotic patients. The 1-year liver-related survival probability for decompensated patients was 52% and for HCC was 63% consistent with prior studies.25–27

Due to the retrospective nature of the study design, detailed information regarding alcohol consumption and the number of patients who had been unsuccessfully treated with HCV antiviral therapy was not available for analysis. Also patient outcome information was extracted from a validated statewide hospital morbidity, mortality and cancer register database using ICD codes. Data linkage accuracy has been shown to be excellent in previous studies; however, there remains the small possibility of miscoding or missing outcomes.

**Conclusion**

The present study has provided new evidence that CHC patients with F0, F1 or F2 fibrosis have a benign course with infrequent episodes of liver-related morbidity and mortality after 15-year follow up. Moreover, those CHC patients with F3 fibrosis had a similar low rate of liver complications during the first 7 years of follow up after which the rate of complications significantly increased. This period probably represents the time required for those with F3 fibrosis to progress to cirrhosis. This information has significant implications regarding the important public health issues surrounding CHC and the potential cost benefits of antiviral treatment.

**Acknowledgement**

We thank Western Australia Data Linkage Unit for patient outcome data extraction.

**References**

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Supporting Information

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

Table S1 Liver-related survival probability for each Metavir stage.

Table S2 Hepatocellular carcinoma (HCC)-free survival probability for each Metavir stage.

Table S3 Liver decompensation-free survival probability for each Metavir stage.
Does the availability of therapeutic drug monitoring, computerised dose recommendation and prescribing decision support services promote compliance with national gentamicin prescribing guidelines?

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Key words
gentamicin, therapeutic drug monitoring, computerised dose prediction, decision support, interviews.

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Abstract

Background: Gentamicin is an aminoglycoside antibiotic that is highly effective in treating Gram-negative infections, but inappropriate use leads to toxicity. In 2010, the Australian Therapeutic Guidelines (Antibiotic) were revised to recommend the use of computerised methods to individualise dosing of gentamicin and optimise therapy, rather than traditional nomogram approaches.

Aim: To determine whether gentamicin prescribing was compliant with the Australian Therapeutic Guidelines, version 14 (2010) in a setting where computerised dose recommendation resources and computerised decision support were available, and to determine why the resources were effective or ineffective in achieving compliance to guidelines.

Methods: During phase 1, a retrospective audit of gentamicin prescribing from 1 January 2012 to 31 December 2012 (n = 826) at a 320-bed teaching hospital in Sydney was undertaken. In phase 2, 12 doctors from specialties with high-volume prescribing of gentamicin were interviewed.

Results: Intravenous gentamicin was used in 545 cases, 81% of which were for short-term therapy (≤48 h). Doctors feared inducing toxicity in patients, but limited the dose rather than altering the dosing interval according to renal function. Of the ‘continued’ dosing cases, 55% went unmonitored and the computerised dose recommendation service was rarely used. Doctors were unaware of its availability despite electronic alerts accompanying prescriptions of gentamicin.

Conclusions: In comparison with the national guidelines, there was significant under-dosing and monitoring practices were haphazard. Computerised electronic alerts were ineffective in informing users. To improve prescribing practices, we recommend exploring alternative computerised decision support approaches (e.g. pre-written orders) and more pervasive and persuasive implementation strategies.

Introduction

Gentamicin is an aminoglycoside antibiotic that retains good activity against multi-drug resistant Gram-negative pathogens. This may be attributed in part to its low rates of use, likely to have been driven by fear of otoxicity and nephrotoxicity.1 Nephrotoxicity is related to cumulative drug exposure. The likelihood of toxicity increases if trough concentrations exceed safe concentrations and if treatment courses are prolonged. Nephrotoxicity associated with these factors is more pronounced in patients with pre-existing renal impairment.2

Once-daily aminoglycoside dosing regimens represent standard practice across most hospitals in Australia. This method of dosing has been shown to be as efficacious and less toxic than former multiple-daily, ‘split’ dosing schedules.3–6 Administering larger doses of gentamicin less frequently, as in once-daily and extended interval regimens, produces higher peak plasma concentrations, enhancing the drug’s bactericidal action, and allows trough concentrations to reach negligible values.
reducing the risk of nephrotoxicity. This regimen changes the shape of the area under the concentration-time curve. Furthermore, this regimen takes advantage of the drug’s long post-antibiotic effect whereby bacterial killing persists well after plasma concentrations fall below bactericidal concentrations.

Although superiority of once-daily dosing of gentamicin has been established, there is wide inter- and intra-patient variability in plasma concentrations.7,8 Therapeutic drug monitoring (TDM) is a proven tool to achieve optimal dosing of gentamicin. Previous versions of the Australian Therapeutic Guidelines9 recommended measuring one gentamicin plasma concentration between 6 and 14 h post-administration. This concentration was used in conjunction with a population-based nomogram to guide dose and dosing interval selection. Although convenient, the nomogram is unsuitable for renally impaired patients or in those with unstable pharmacokinetics, which is often the situation in sick patients.10 Using the nomogram in these situations can result in sub-therapeutic gentamicin concentrations, leading to unresolved or resistant infection, or supra-therapeutic concentrations, resulting in serious toxicity.11

Changes to the Australian Therapeutic Guidelines: Antibiotic, version 14,12 recommend that intravenous gentamicin therapy be initiated empirically in most patients. TDM is not required for empirical use of the drug that by definition does not exceed 48 h of therapy. However, if dosing continues past 48 h (also to be referred to as ‘continued’ therapy), ‘directed therapy’ is advised. Directed therapy is limited to a small number of indications, including infections when resistance to other safer antimicrobials has been shown, combination therapy for serious Pseudomonas aeruginosa infections, brucellosis, and in low doses as synergistic treatment with other antibiotics for infective endocarditis. ‘Directed therapy’ requires TDM to commence at the last empirical dose (at 48 h). The gentamicin plasma concentrations are then used to calculate the area under the gentamicin concentration-time curve and predict subsequent doses. The new guidelines only endorse computer-derived dosing recommendations. Retrospective studies provide theoretical evidence of the positive impact of computerised dose predictions on clinical outcomes;13 however, there is limited prospective work demonstrating that doses based on software recommendations result in better clinical outcomes than those based on clinical judgement. An urgent need for prospective clinical trials in this area has been identified.14

Although several gentamicin audits have been conducted, the majority of these15–18 were prior to 2010, before the version 14 update. The focus of these audits was largely to review and compare multiple-daily dosing against once-daily dosing regimens. Little is known about compliance with the Australian Therapeutic Guidelines, version 14 in particular the impact of computerised dose recommendations. Since 2010, two audits have been reported, neither of which was conducted at a site that had computerised dose recommendation in place.14,19 Both these studies found gentamicin dosing discordant with the guidelines. Furthermore, a telephone survey of key stakeholders at 18 Australian hospitals in 2012 found that the majority were aware of the 2010 changes to the national guidelines, but only 5/18 participating hospitals had implemented the new guidelines by replacing the nomogram with computerised dosing recommendations for patients undergoing continued gentamicin therapy.20

This study therefore aimed to determine whether gentamicin was being prescribed in accordance with the Australian Therapeutic Guidelines: Antibiotic, version 14 at a teaching hospital in Sydney, Australia, where all the endorsed resources were in place, in particular, computerised dose recommendation software for continued therapy as well as an electronic-prescribing system with decision support and electronic alerts. We also set out to determine why the resources were effective or ineffective in achieving compliance to guidelines. To do this, we explored prescriber opinions of gentamicin therapy, the TDM services and computerised dose recommendation and decision support services.

Methods

Hospital setting and e-prescribing

The study was conducted at a teaching hospital in Sydney, Australia with approximately 320 beds. At the time of the study, a gentamicin-dosing advice service had been available from the clinical pharmacology division of the pathology service of the hospital for approximately 18 months (since June 2011). This service included TDM reporting and provided personalised patient-dosing recommendations through the technique of Bayesian pharmacokinetic prediction software, Abbotbase (version 1; Abbott Diagnostics, Chicago, IL, USA) (computerised dose recommendation). Additionally, all in-patient wards at the hospital, except for the emergency department (ED), used an electronic-prescribing system, MedChart (versions 4.2 (1 January–10 December) and 5.3 (10–31 December); http://www.isothealth.com).

MedChart presents a range of computerised alerts to prescribers at the point of ordering a medication (e.g. allergy warnings, therapeutic duplication alerts). Prescribers are informed of the availability of the dosing service through the presentation of an alert when gentamicin is prescribed (Fig. 1). This alert includes a statement that the prescriber should refer to an
‘Aminoglycoside Prescribing Information’ sheet (hyperlinked to the pathology website), a notice that TDM is required for courses longer than 3 days (last ‘empirical’ dose at 48 h), and pager extensions to the relevant microbiology and clinical pharmacology consultants. This alert does not restrict prescribing of the aminoglycoside.

**Study design**

This study comprised two phases: (i) a retrospective audit of gentamicin prescribing and (ii) interviews with prescribers.

The study was approved by the Human Research Ethics Committee at the University of New South Wales and the hospital.

**Study procedure**

**Phase 1. Retrospective audit**

The first phase was a retrospective audit of data retrieved from the hospital’s electronic information systems. All inpatients (except ED) that were prescribed intravenous gentamicin between 1 January 2012 and 31 December 2012 were included in the audit. Each patient was assigned a unique case number according to his or her stay at the hospital (based on admission and discharge dates) to aid analysis and preserve patient confidentiality. There were no exclusion criteria. Gentamicin was available in 80 mg/2 mL vials and was mostly stored on imprest on the majority of wards. Patient demographics, renal function, specialty of admitting doctor, gentamicin dose, route and administration frequency as well as TDM collections were retrieved from the hospital’s clinical information systems.

Each gentamicin case (dosing and management practice) was evaluated against the most recent national guidelines, the *Australian Therapeutic Guidelines: Antibiotic, version 14*. Compliance to empirical dosing (dosing between 0 and 48 h) was assessed in the following ways: (i) was the initial dose appropriate (age and weight based), (ii) was the subsequent dose appropriate (this dose should be the same as the initial dose) and (iii) was the dosing interval appropriate (based on the patient’s...

![Figure 1](image-url)
creatinine clearance)? Compliance to directed therapy (>48 h) was assessed as follows: (i) was a request for TDM made and (ii) was the timing and frequency of TDM collections appropriate (first concentration; end of infusion and second concentrations; 6–14 h post-dose)? Patient bodyweights were not recorded by clinicians in the hospital’s clinical information systems, making it difficult to evaluate directly the appropriateness of initial administered doses. A surrogate marker, estimated ideal bodyweight (eIBW), was used instead, with the expectation that marked under- or over-dosing would be revealed by an extreme eIBW. The eIBW was back calculated from the gentamicin dose administered and the recommended empirical dose (age and weight based) as follows:

$$eIBW\ (kg) = \frac{\text{Initial dose (mg)}}{\text{Recommended initial dose (mg/kg)}}.$$  

It was assumed that the maximum possible dose for a patient’s age and bodyweight was administered. For example if a 60-year-old patient was administered a gentamicin dose of 280 mg, their eIBW was 70 kg (280 mg / 4 mg/kg). The age-stratified distribution of the eIBW was compared with the IBW calculated for the Australian population (Australian Health Survey, Australian Bureau of Statistics, http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4364.0.55.0012011-12?OpenDocument)

The Australian Therapeutic Guidelines recommend that creatinine clearance be calculated using the Cockcroft and Gault method (using total or ideal bodyweight). As the patient weights were unavailable, estimated glomerular filtration (Modified Diet in Renal Disease formula) was used in place of creatinine clearance. A leeway of 6 h was given in the assessment of the appropriateness of the dosing interval.

**Statistical analysis**

Data management, basic statistical calculations and analyses were performed using Office Excel 2010 (Microsoft, Redmond, WA, USA) and figures were generated in GraphPad Prism, version 6.02 (GraphPad Software, San Diego, CA, USA). Descriptive statistics were used to determine the proportion of patients receiving appropriate gentamicin therapy as described above.

**Phase 2. Interviews**

In Phase 2, short, semi-structured interviews with prescribers were conducted. ‘High use’ specialties/units were identified from Phase 1, and individual doctors from each Phase 2. Interviews unit were invited to participate in an interview through email. High use specialties were units responsible for more than 40% of gentamicin prescribing over the study date range (Table 1). There were 12 of the 19 doctors who were contacted and agreed to be interviewed. The participants included nine consultants, two registrars and one resident in the areas of orthopaedics, haematology, geriatrics, palliative care, gastroenterology and lung transplant. The interview questions appear in Table S1. The interviews were audiotaped and transcribed. Interviews continued until theme saturation was achieved (as assessed by two investigators). The de-identified content was reviewed and analysed by two investigators to identify recurring themes.

**Results**

**Phase 1: Retrospective gentamicin audit**

Our patient population had a median age of 62 years with moderate renal impairment (median estimated glomerular filtration rate (eGFR), 82 mL/min). A majority of gentamicin doses were stat doses (70%). A summary of our study population and gentamicin cases is shown in Table 1.

### Table 1 Demographics of study population and overview of gentamicin therapy

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Median age (IQR) years</th>
<th>Median eGFR (IQR) (mL/min)</th>
<th>Males (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>62 (47–75)</td>
<td>84 (60–111)</td>
<td>303/545 (55.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overview of gentamicin therapy</th>
<th></th>
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<tbody>
<tr>
<td>Cases† (n)</td>
<td>545</td>
<td></td>
</tr>
<tr>
<td>Empirical cases; ≤48 h dosing (%)</td>
<td>477 (87.5)</td>
<td></td>
</tr>
<tr>
<td>Stat doses (%)</td>
<td>335/477 (70.2)</td>
<td></td>
</tr>
<tr>
<td>Continued cases; &gt;48 h dosing (%)</td>
<td>68/545 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Prescriptions (n)</td>
<td>826</td>
<td></td>
</tr>
<tr>
<td>Administrations (n)</td>
<td>975</td>
<td></td>
</tr>
<tr>
<td>Most common dose, mg (%)</td>
<td>240 (39.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Top five prescribing specialties</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Haematology (%)</td>
<td>120/545 (22.0)</td>
<td></td>
</tr>
<tr>
<td>Orthopaedics (%)</td>
<td>110/545 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Geriatrics (%)</td>
<td>44/545 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Heart and lung transplants (%)</td>
<td>40/545 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Other surgical units‡ (%)</td>
<td>39/545 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Other medical units (%)</td>
<td>192/545 (35.2)</td>
<td></td>
</tr>
</tbody>
</table>

†Cases defined by in-patient stay and could include more than a single prescription and therefore also possibly multiple administrations. ‡Other surgical units, colorectal, gastrointestinal, ‘ear, nose and throat’, neuro-, plastic and reconstructive, and vascular surgery. eGFR, epidermal growth factor receptor; IQR, interquartile range;
Appropriateness of decision-making in empirical therapy

Patient eIBWs appeared to be normally distributed with peaks at around 40 kg for the youngest group, 50 kg for the middle-aged group and 60 kg for the older group (Fig. 2). Compared with estimates of IBW derived from 2012 Australian National Health Survey data, our averages were lower in younger age groups suggesting that under-dosing of gentamicin was common in these groups. The majority of subsequent empirical doses were appropriate (91%), as were most dosing intervals on the basis of patients’ renal function (73%) (Table 2).

Appropriateness of decision-making in continued therapy

Of the continued therapy cases, 56% (38/68) went unmonitored; that is, TDM was not performed. As shown in Table 2, the TDM requests that were made were incorrect with respect to frequency of ordering and timing of blood samples. The computerised dose recommendation service was accessed in only 4 of the 30 monitored and continued therapy TDM cases, but only one of these dose recommendations was actioned, in the form of a dosage change, by the prescriber. In addition, we found that of all TDM requests made (n = 100), the majority (60%) were unnecessary according to the guidelines as they occurred during empirical therapy.

Phase 2: Interviews with prescribers

Doctors reported that they based their first dose of gentamicin on their patient’s bodyweight. When prompted, doctors said that ideal bodyweight was used; however, it was unclear how this was calculated because most stated that weight (and height) was rarely recorded. Less than half of the doctors mentioned age as a patient characteristic that would be considered when deciding what first dose to prescribe, but almost all mentioned renal function. Only two doctors said that they would repeat the initial dose and change the dosing interval according to renal function if empirical therapy was to continue past a stat dose. Many made reference to ‘dose adjustment’ using the nomogram, even in empirical therapy.

Although all doctors were aware of gentamicin-induced nephrotoxicity and ototoxicity, few had experienced it in their patients. Most noted that conservative prescribing habits stemmed from fear of toxicity. One doctor said, ‘. . . Because I am very conscious of the side effects . . . I would tend to go on the lower side . . . and I think that most of my colleagues would tend to go on the lower side of the dose, and even scale it down sometimes’.

Figure 2 (a–c) Age-stratified estimated ideal bodyweight (eIBW) distributions for gentamicin cases at this study hospital in 2012. Patient eIBW (solid lines) were calculated using the initial dose (mg) and the age-stratified dosing algorithm (mg/kg) recommended by the Australian Therapeutic Guidelines: Antibiotic, version 14. All intravenous gentamicin cases were included in the analysis. (a) 10–29 year group (range = 18–29 years, n = 39), (b) 30–60 years (range = 30–60 years, n = 225) and (c) greater than 60 years (range = 60–110 years, n = 566). For each age group the Australian average ideal bodyweight (dashed lines) was overlaid. The Australian data were taken from the 2011–2012 Australian Health Survey.
There was very poor knowledge and understanding of the place of TDM for safe and effective aminoglycoside therapy. There was also confusion surrounding the appropriateness of TDM timing and frequency in continued therapy. The majority of doctors said that one blood sample is needed after each dose to measure the ‘trough level’ and very few referred to taking a sample for peak concentration measurement. There was also inconsistency in doctors’ opinions of an appropriate time window to take these samples. One doctor said that a trough level could be measured at 24 h after the dose and others said 14 h. Another doctor said that a peak level could be measured 6 to 8 h after the dose.

Most doctors had not used the computerised dose recommendation service that was accessible through the electronic-prescribing system because they were not aware that it was available. Instead, they referred to the traditional approach of using a nomogram and thus a dose adjustment method in directed therapy. One doctor noted that the service was not used because it was difficult to access, ‘You know, it might be set up, but from a clinical practice point of view it’s buried in the minutiae somewhere, and if it takes 20-min to find it, nobody’s going to use it’. Some doctors mentioned that they were not aware of the alert that appears when they prescribe gentamicin and suggested that tailoring alerts to the prescriber’s usage pattern may safeguard against ‘alert-fatigue’.

**Discussion**

This gentamicin audit was conducted to evaluate prescribing compliance with the *Australian Therapeutic Guidelines: Antibiotic, version 14* given the availability of computerised decision support, including computerised dose recommendation. The main finding was that the availability of all recommended resources did not result in doctors complying with guidelines. We found that although prescriber compliance in some areas was high, it was poor in other areas. That is, prescribers selected appropriate dosing intervals in the majority of cases, but under-dosing was a significant problem, as were TDM practices in support of safe and effective continued therapy.

Both phases of this study identified under-dosing as a problem with the most commonly prescribed dose of gentamicin observed to be 240 mg. In previous Australian audits, with similar patient demographics, the most prevalent dose was also found to be 240 mg.14,15,19 In these studies, the authors suggested that physicians might have based dosing on the ‘look’ of the patient rather than a calculation based on IBW. Our interviews confirmed this hypothesis: patient weights were not typically measured or recorded by doctors. Furthermore, doctors expressed fear of toxicity in patients and a consequence of this was conservative dosing or ‘dose-reduction’. This is a crucial finding as under-dosing ultimately leads to sub-therapeutic drug levels in patients, potential development of resistance and compromised treatment efficacy, as well as potential prolonged therapy duration and subsequent toxicity from increased aminoglycoside exposure. These negative outcomes were not raised by any of our participants during interviews suggesting that education of prescribers on the consequences of conservative dosing is needed.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Therapeutic guidelines information†</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial empirical dose compliance (%)</td>
<td>The first dose is weight-based and stratified by age.</td>
<td>Could not be assessed directly; eIBW was calculated as a surrogate measure for appropriate initial dose.</td>
</tr>
<tr>
<td>Subsequent empirical dose compliance (%)</td>
<td>Subsequent empirical doses (0 h &lt; t ≤ 48 h) are the same as the first dose.</td>
<td>91.4% (498/545)</td>
</tr>
<tr>
<td>Empirical dosing interval compliance (%)</td>
<td>Dosing interval is determined by CrCl‡.</td>
<td>72.8% (206/283)</td>
</tr>
<tr>
<td>Compliance to directed therapy</td>
<td>TDM is only required for continued (&gt;48 h) intravenous therapy.</td>
<td>44.1% (30/68)</td>
</tr>
<tr>
<td>TDM request compliance (%)</td>
<td>For each dose administered after 48 h, two samples were taken in the following windows: end of infusion and 6–14 h</td>
<td>0%</td>
</tr>
<tr>
<td>TDM procedure compliance (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Australian Therapeutic Guidelines: Antibiotic, version 14. ‡Patient weight was unavailable, estimated glomerular filtration rate (Modified Diet in Renal Disease) was used instead. A 6 h leeway was given for assessing compliance for this outcome. CrCl, creatinine clearance; eIBW, estimated ideal bodyweight (initial dose (mg)/initial recommended dose (mg/kg)); TDM, therapeutic drug monitoring.
Compliance to the guidelines with respect to directed therapy recommendations was particularly poor as was use of TDM services for this prolonged therapy. A significant proportion of continued cases went unmonitored and in the few cases where TDM was used, it was not used appropriately. These findings are in contrast to a recent audit on TDM practices across two teaching hospitals, which showed that 80% of cases monitored were appropriate in terms of timing and frequency. This inconsistency may be due to more rigorously applied local guidelines/protocols at these study hospitals. Ensuring that monitoring occurs only in continued cases could not only help to reduce hospital costs, but also avoid unnecessary blood sampling. Our interview findings indicated that there was confusion among doctors regarding when and why monitoring was needed and very few doctors were aware that the computerised dose recommendation service existed. These findings, coupled with the poor knowledge and often outdated views of appropriate dosing expressed by doctors, suggest that education (and re-education) is critical. Informing prescribers of the benefits of appropriate gentamicin dosing and the need for TDM, through the distribution of materials (e.g. posters), presentations (e.g. grand rounds, orientation) and where possible, one-on-one education, may be needed to result in more appropriate use of gentamicin.

Our findings also demonstrate that computerised alerts embedded into the electronic-prescribing system were ineffective in informing doctors of the services available and in directing doctors to further information. Previous research has shown that although computerised alerts have the potential to influence prescribing behaviours, systems often generate excessive numbers of alerts and the result is that most alerts are overridden by users. This has been shown to be the case at our study hospital. Although the hospital uses electronic prescribing, the full potential of e-prescribing is not currently being realised. Several additional functions or features could be incorporated into the system to ensure that dosing is appropriate and usage is monitored. Providing users with passive information (i.e. a link to guidelines) is unlikely to be as effective as more interruptive or active decision support. For example, pre-written orders for gentamicin that include appropriate initial doses (based on IBW) and automatically cease following three days, could be incorporated into the electronic system, as could hard-stop alerts triggered following empirical therapy, preventing continued therapy unless TDM is initiated.

This study was conducted at one site with no paediatric or maternity services, which limits generalisability to other hospital settings, but as one of the first hospitals in Australia to adopt all recommended resources and electronic prescribing, this work highlights some general lessons for other sites contemplating implementation of these services. We did not audit patient notes or microbiology data, and this limited our ability to evaluate indications, thus determine compliance in special cases, such as infective endocarditis where dosage and frequency differ. Patient health outcomes were not assessed in our audit, and it was therefore not possible to assess the impact of the under-dosing we observed. Another limitation is that few junior doctors were interviewed and so their awareness of the guidelines and of the services available at the hospital was not evaluated.

**Conclusion**

Overall, we identified significant under-dosing of intravenous gentamicin and haphazard monitoring practices. On-going education of both senior and junior doctors would ensure prescribing practices evolve with new research and clinical experience. This is especially relevant to old-generation drugs, such as the aminoglycosides, where selecting the right dose early in therapy is critical. Computerised decision support, in the form of alerts embedded in electronic-prescribing systems, although an apparently good platform for information dissemination to doctors, has not been effective in this setting, highlighting the complexity associated with the design of effective alerting for doctors. We recommend exploring alternative computerised decision support approaches (e.g. pre-written orders) and more widespread implementation strategies (i.e. effective education, prescriber feedback). The study hospital is now exploring these alternative approaches. This study has demonstrated the persistence of non-compliant gentamicin prescribing practices following provision of all recommended resources and the challenges associated with ensuring that patients receive their optimal, individualised dose of gentamicin.

**References**


**Supporting information**

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

| Table S1 | Phase 2 semi-structured interview questions. |

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Different genetic impact in the development of renal length and width: a twin study

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Key words
renal length, heritability, twin, sonography, lifestyle.

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Abstract

Background: Ultrasound measurements of renal dimensions are conventionally limited to renal length, shape and cortical thickness. These are regarded as adequate for normal therapeutic decision-making and volume measurements are reserved for a few clinical trials. However, there is no evidence concerning the degree to which renal length or volume is independently susceptible to heritable and environmental influences.

Aim: We aimed to determine whether renal length or width (as a surrogate of volume) was more influenced by heritability.

Methods: A single operator measured renal length and width in 114 adult monozygotic and same-sex dizygotic Hungarian twin pairs (mean age 43.6 ± 16.3 years), using an Esaote MyLab 70X ultrasound machine with curved array transducer (1–8 MHz, CA431).

Results: Analysis of within-pair co-twin correlations adjusted for age and gender showed that the age- and sex-adjusted heritability of average renal length was 51% (95% confidence interval, 29–72%). Renal width showed negligible genetic influence. Common environmental effects had no influence, and unshared environments were responsible for 49–80% of the variance, mainly renal width.

Conclusions: This study is the first to demonstrate the moderate heritability and limited environmental influence on renal length, and the contrasting lack of heritability of renal width, which is mainly influenced by unshared environmental components, that is lifestyle habits. Renal width therefore better represents the influence of modifiable environmental factors than renal length. The results suggest that renal width not length should be reported to facilitate early detection and monitoring of renal disease.

Introduction

Renal length, more commonly than renal volume, is a widely measured clinical parameter providing information on the underlying disease process and the potential reversibility of kidney damage. 1,2 Changes in renal length, width, volume and cortex width are often observed in patients presenting with acute and chronic kidney dysfunction, in hypertension-, diabetes- and renal insufficiency-related renal artery stenosis, in the evaluation and follow-up of kidney transplant recipients, in recurrent urinary infections and vesicoureteric reflux. 3,4 The renal dimensions also allow conclusions as to the single kidney glomerular filtration rate to be made. 5

It has been shown that kidney size is influenced by complex factors, including body mass index (BMI), height, gender, age, position of the kidneys, stenoses and number of renal arteries. 6 Renal dimensions, such as parenchymal volume, an important index for clinical decisions, can be also assessed by non-enhanced multidetector computed tomography (CT). 7 Cortical volume magnetic resonance imaging (MRI) measurements have also been reported, and the cortical volume can be calculated from voxel counting, a technique where areas of high-signal renal cortex are extracted from the rest of the kidney. 8 Sonographically, the most exact measurement of renal size is renal volume, but clinically, measurement of renal length is most practical and can be done in prone or supine position. 9

Ultrasound measurements of renal dimensions are conventionally limited to renal length, shape and cortical thickness. Since therapeutic decisions are frequently based on the results of these measurements, clarification
of underlying mechanism of renal length or width is of increasing importance. Renal length was recently shown to have a significant genetic background in a family study independently of age and body size, exact magnitude of the genetic and environmental effects is still unclear. In addition, there are no data on the heritability of renal width and no evidence exists concerning the degree to which renal length or volume is independently susceptible to heritable and environmental influences. Therefore, we aimed to assess how much the renal length and width are influenced by modifiable environmental factors and how large the genetic predisposition is.

Methods

Study design

A total of 69 monozygotic and 45 same-sex dizygotic Caucasian twin pairs above 18 years of age were recruited from the Hungarian Twin Registry for an abdominal ultrasound in the Department of Radiology and Oncotherapy, Semmelweis University in 2009 and 2010. Subjects were requested to drink fluid and avoid eating 1 h and drinking coffee or alcohol 6 h prior to the testing. We excluded opposite-sex dizygotic twin pairs to avoid bias of the heritability estimates in the presence of gender-specific or X chromosome effects, pregnant subjects and patients with acute or chronic renal disease. To determine zygosity, a multiple-choice self-reported seven-part questionnaire was used. Risk factors, history of cardiovascular and renal diseases were all recorded. The study was approved by the Ethical Committee of Semmelweis University and conducted in full compliance with regulations of the Declaration of Helsinki. All participants gave informed consent.

Renal ultrasound

Renal grey-scale ultrasonography was performed (Esaote MyLab 70X Vision, Esaote SpA, Genoa, Italy; equipped with a curved array transducer, 1–8 MHz, CA431). The grey-scale amplification gain, the time-gain compensation curve and focus number (adjusted at the level of the kidney) were adjusted to acquire the best images of the kidneys. All the examinations were performed by the same experienced sonographer. All the twin subjects were well hydrated and had full bladders at the time of examination. Renal measurements were performed with patients in the supine position or in the contralateral decubitus position. Sagittal and axial plane images were obtained either using a subcostal approach with the patient in the supine position, or from the contralateral decubitus position view, using a posterior approach with the patient in the contralateral decubitus position. The longitudinal dimensions were measured in a section visually estimated to represent the largest longitudinal section. The width was measured in a section perpendicular to the longitudinal axis of the kidney as assessed from the longitudinal plane. The level of the transverse section was at the vascular hilum of the kidney. Pole-to-pole kidney length and the largest width in the middle third of the kidney were measured with electronic calipers bilaterally at the time of scanning.

Statistical analysis

Descriptive analysis (mean, standard deviation, percentage for categorical variables) was carried out by spss statistics 17 (spss Inc., Chicago, IL, USA). Monozygotic (MZ) and dizygotic (DZ) subsamples were compared using independent samples t-tests. All parameters showed a normal distribution, and outliers were excluded from the analysis. In case of renal length, we used the average value of both kidneys. The descriptive estimate of the genetic influence in monozygotic and dizygotic pairs was calculated using the within-pair co-twin correlations adjusted to age and gender. Substantially higher MZ co-twin correlation (compared with DZ correlations) suggests heritability, whereas similar co-twin correlations imply that shared environmental components drive the variance more strongly. Based on similarities between MZ and DZ twins, structural equation modelling (A-C-E model) was carried out by Mplus Version 6.1 (Muthén & Muthén, Los Angeles, CA, USA) in order to decompose the variation (across individual) into sources attributable to additive genetic effects (A), common (or shared) environment (C) and unshared (or unique) environment (E). (For a very introductory review of the procedure written for social scientists uninitiated in the field of biometrics, see Medland and Hatemi 2009) Empirical confidence intervals were calculated with a Bollen-Stine Bootstrap. All inferential statistics were estimated using full information maximum likelihood. P-values lower than 0.05 were considered significant.

Results

Descriptive analysis

Mean age was 43.6 ± 16.3 years, and 73% of the participants were female. Hypertension, hypercholesterinaemia and diabetes were present in 32, 22 and 6%. Of the subjects, 17% and 14% were active and former smokers, respectively. Mean BMI indicated 25.7 ± 4.9 kg/m². There were no significant differences between monozygotic and dizygotic twins in these variables and the measured renal
dimensions, except right kidney’s width, which was larger in DZ twins (4.4 ± 0.5 cm vs 4.2 ± 0.6, P < 0.05). The mean average renal length, width of the left and right kidneys was 9.6 ± 1.0 cm, 4.9 ± 0.7 cm and 4.3 ± 0.6 cm, respectively. Mean right and left renal lengths showed a moderate correlation (r = 0.373, P < 0.001). Pearson correlation between average renal length and left and right width indicated r = 0.393 and r = 0.335 (P < 0.001). Subjects with hypercholesterinaemia and hypertension had smaller average renal length (9.3 ± 1.1 cm vs 9.7 ± 0.9, P < 0.05 and 9.4 ± 1.1 cm vs 9.7 ± 0.9, P = 0.08). Active smokers had smaller renal width on the right (4.1 ± 0.4 cm vs 4.3 ± 0.6, P < 0.05). There was no further significant relationship between renal dimensions and BMI, cigarette smoking, hypertension, diabetes and hypercholesterinaemia.

**Univariate analysis**

Monozygotic co-twin correlations were higher than of dizygotics in case of average renal length, indicating that age- and sex-adjusted heritability was 51% (95% confidence interval (CI), 29–72%) (Table I). Renal width showed negligible, insignificant genetic effects. Common environmental effects had no major influence, and unshared environments were responsible for 49–80% of the variance especially in case of renal width.

**Discussion**

To our knowledge, our results are the first to demonstrate the moderate heritability and limited unique environmental influence of renal length, and the contrasting lack of heritability of renal width, which is mainly influenced by unshared environmental components, that is lifestyle habits in a healthy twin population.

Previous studies have postulated that some genes play a role in kidney size in newborns;19–21 however, there have been limited reports on the magnitude of these genetic effects to date. There is only one recently published article that has assessed the heritability of renal length. In that study, there were 205 randomly selected Swiss nuclear families and the adjusted heritability estimate of renal length was 47.3 ± 8.5%, highlighting the familial aggregation of this trait independently of age and body size.2 It must be taken into consideration that the family studies are useful in the determination of inter-generation resemblance or difference, but, in contrast to the twin study design, have a serious limitation that they cannot tangibly express outside factors, such as family environment and culture.22 Therefore, family studies cannot reliably distinguish the heritability and common environmental effects. Compared with the family study

---

Table 1: Parameter estimates for additive hereditary (A), common environment (C) and unique environmental influences (E) on renal length and width by structural equation modelling in 69 monozygotic and 45 dizygotic twin pairs

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>AIC</th>
<th>BIC</th>
<th>-2LL</th>
<th>Degrees of freedom</th>
<th>P-value of χ² difference</th>
<th>χ² difference</th>
<th>A-C-E</th>
<th>A-E</th>
<th>C-E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average renal length¶</td>
<td>610.241</td>
<td>626.552</td>
<td>598.24</td>
<td>0</td>
<td>1</td>
<td>0.0001</td>
<td>0.545 (0.344, 0.737)</td>
<td>0.032 (−0.334, 0.329)</td>
<td>—</td>
</tr>
<tr>
<td>Width of left kidney¶</td>
<td>463.329</td>
<td>479.640</td>
<td>451.328</td>
<td>0</td>
<td>0</td>
<td>0.0001</td>
<td>0.254 (0.065, 0.461)</td>
<td>−0.064 (−0.378, 0.320)</td>
<td>—</td>
</tr>
<tr>
<td>Width of right kidney¶</td>
<td>400.144</td>
<td>416.561</td>
<td>388.144</td>
<td>0</td>
<td>0</td>
<td>0.0001</td>
<td>0.340 (−0.000, 0.484)</td>
<td>−0.078 (−0.195, 0.040)</td>
<td>—</td>
</tr>
</tbody>
</table>

Where one of the A-C-E model fit significantly worse but the other did not, we selected the model that did not fit significantly worse. When neither A-C nor C-E models fit significantly worse, we selected the A-E model. A-C-E model fit significantly worse but the other did not, we selected the model that did not fit significantly worse. When neither A-C nor C-E models fit significantly worse, we selected the A-E model. A-C model fit significantly worse but the other did not, we selected the model that did not fit significantly worse. When neither A-C nor C-E models fit significantly worse, we selected the A-E model. A-C-E model fit significantly worse but the other did not, we selected the model that did not fit significantly worse. When neither A-C nor C-E models fit significantly worse, we selected the A-E model. A-C model fit significantly worse but the other did not, we selected the model that did not fit significantly worse. When neither A-C nor C-E models fit significantly worse, we selected the A-E model. A-C-E model fit significantly worse but the other did not, we selected the model that did not fit significantly worse. When neither A-C nor C-E models fit significantly worse, we selected the A-E model. A-C model fit significantly worse but the other did not, we selected the model that did not fit significantly worse. When neither A-C nor C-E models fit significantly worse, we selected the A-E model. A-C-E model fit significantly worse but the other did not, we selected the model that did not fit significantly worse. When neither A-C nor C-E models fit significantly worse, we selected the A-E model.
of Pruijm et al., inter-generation resemblance did reside in genetic heritability since we found a similar heritability estimate. Our findings indicated that common environmental factors, that is diet, familiar socialisation, exposure to high levels of air pollution and shared womb, are not responsible for the total variance of renal length. In contrast, unique environmental components accounted for the major variance, and these lifestyle factors, such as smoking, unhealthy nutrition and lack of physical activity can be prevented and modified.

Besides loss of glomeruli and previous inflammations, it has been shown that the kidney becomes relatively wider and thicker by ageing, possibly due to the relaxation of the abdominal wall with age indicating broadening. We failed to find significant genetic influence on the renal width, and unique environment was responsible for the determination of this trait (74–80%), similar to our previous work where we reported a negligible role for the heritability of renal parenchymal thickness and mainly unshared environmental effects accounted for 70% of the studied variation. These findings support the view that renal parenchymal thickness and renal width changes may be first and foremost acquired through environmental effects, underscoring the importance of lifestyle in primary prevention in contrast to the renal length, whose measurement is most practical in everyday situations with ultrasound and clinically more relevant for therapeutic decisions. This kind of view of different genetic determination has never been described, and subsequent genetic studies are necessary. An MRI study noted that the correlation of kidney length versus cortical volume was worse than the correlation of kidney length versus total kidney volume in patients with renovascular disease. As kidney size correlates positively with the number of glomeruli and the number of glomeruli correlates with kidney function, we also hypothesise that families inheriting a relatively large kidney might be genetically ‘protected’ against kidney function deterioration with ageing, as negoitated by Pruijm et al. Taking into account findings of Pruijm et al. and our own results in a clinical perspective, renal width or parenchymal thickness better represent the effects of modifiable environmental factors than kidney length or volume, which are moderately heritable. Therefore, we speculate that radiological reports should include renal width or parenchymal thickness not renal length or volume. It would make the diagnostics more effective, allowing possibility of detection of renal diseases in relatively early stages and their prevention by lifestyle habit changing.

This study should be interpreted within the context of its strengths and limitations. Ultrasonography has a weakness of its two-dimensional nature and operator dependency. Ultrasound was found to be relatively equal in the assessment of renal dimensions compared with CT. On the other hand, other studies demonstrated the superiority of CT- or MRI-based methods to assess kidney volume against ultrasound. We have tried to minimise variability of ultrasound measurements by utilising a single sonographer for all measurements. Unfortunately, only a single person assessed each individual, and therefore, we have little information concerning possible measurement error in the measurement. This could lead to non-differential misclassification and potentially bias the study towards the null hypothesis of no genetic effect.

Of note, first, the hydrated state of the participants, variations in the position and rotation of the kidneys, possible dystopia and extrarenal pyelon can also influence the results. Second, the relatively small number of participating dizygotic twins may lead to statistical errors in the ACE analysis by increasing the E variance. The same reason did not allow us to test genetic-environmental interactions. Third, we did not use the body surface area, a well-known influencing factor for kidney volume, as we assessed the more common BMI in our subjects. Moreover, kidney function was not measured, and therefore, no adjustment for these variables was done in the genetic analysis. No estimate of renal excretory function or proteinuria was performed in study participants. Furthermore, several participants had risk factors for chronic kidney disease including a diagnosis of hypertension in 32% and a diagnosis of diabetes in 6%. Therefore, failure to exclude adequately the presence of individuals with chronic kidney disease or other variables that could modify renal size, potentially confound the results. Due to the small sample size, we could not afford to reduce our variation with controls that go beyond age and sex (the only truly environmental and the only truly genetic predictor). It could be argued that additional controls such as height, BMI or body surface area could have been used. There is a debate in twin studies on the value of assessing controlled and uncontrolled variation. Although we are not taking sides in this debate, due to our sample size, we chose not to eliminate valuable variation through plausible controls and decided to assess kidney length/width in its raw form.

The major strengths are the twin design due to the advances described above and that the same sonographer investigated both members of a twin pair.

**Conclusion**

This study is the first to demonstrate the moderate heritability and limited unique environmental influence of renal length. There is a lack of heritability on renal width because it is mainly driven by unshared environmental components, that is lifestyle habits. Accordingly, renal
Heritability of renal length and width seems to represent better the effects of modifiable environmental factors than kidney length. Therefore, further studies should confirm whether assessment of renal width instead of length would better indicate the harmful environmental effects on kidney size, allowing possibility of earlier detection of renal diseases.

References


Echocardiographic and electrocardiographic findings in patients with obesity hypoventilation syndrome

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Key words
cardiovascular disease, echocardiography, left ventricular hypertrophy, obesity hypoventilation syndrome, obstructive sleep apnoea.

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Abstract

Background: Obesity is a risk factor for both sleep-related breathing disorders (SRBD), including obesity hypoventilation syndrome (OHS) and cardiovascular diseases (CVD). The development of CVD in patients with SRBD is usually attributed to the fact that most patients are obese in addition to conventional cardiovascular risk factors.

Aims: This study aims to measure the prevalence of certain CVD in patients with OHS in the Auckland region and highlight the importance of the effects of SRBD on the heart.

Methods: A dataset of all patients with a formal diagnosis of OHS that were under active follow up was compiled from Auckland District Health Board Sleep Disordered Breathing Service. Clinical notes were retrospectively reviewed for echocardiogram reports, blood pressure measurements and electrocardiograms.

Results: Forty-seven patients were included in the present study. The median age was 60 years, 24 were female (51%), 20 (42.5%) had diabetes, mean HbA1C was 53.5 mmol/mol, mean systolic blood pressure was 127 mmHg, mean body mass index was 49 kg/m2, mean forced expiratory volume in 1 s was 1.7 L, mean estimated glomerular filtration was 71 mL/min/1.73 m2 and there was anti-hypertensive use in 31 (65.9%) patients. Thirty-three patients had poor quality echocardiography views (70.2%). Left ventricular systolic and diastolic function was impaired in 8 (25%) and 18 (60%) respectively. Right ventricular dysfunction and pulmonary hypertension was present in 19 (63.3%) and 13 (52%) respectively. Sixteen patients (34%) had recurrent atrial or ventricular arrhythmias.

Conclusion: There appears to be a high prevalence of right ventricular impairment, pulmonary hypertension, left ventricle hypertrophy, diastolic dysfunction and arrhythmias in patients with OHS. These findings would appear to be higher than expected in obese patients without OHS. A larger prospective matched cohort study would be needed to confirm the clinical significance of these findings.

Introduction

Obesity hypoventilation syndrome (OHS) is defined by the presence of day-time alveolar hypoventilation that results in carbon dioxide retention (PaCO2 > 45 mmHg) occurring in obese patients with body mass index (BMI) of more than 30 kg/m2 in the absence of any other disease associated with alveolar hypoventilation to explain their hypercapnia.1 There is a high prevalence of obstructive sleep apnoea (OSA) in patients with OHS (90%), and they often present with similar symptoms. Conversely, in a few retrospective series, the prevalence of OHS in OSA ranged from 9% to 14%.2-4 The mechanism by which patients with OSA develop OHS is uncertain, but it has been suggested that altered respiratory drive and chronic exposure to hypoxia caused by nocturnal apnoea/hypopnoea episodes combined with increased work of breathing during sleep leads to hypoventilation in a subset of patients.2 Therefore, those patients with OHS often but not invariably have more severe OSA than patients with OSA with normal PaCO2 and tend to have a longer history of a sleep-related breathing disorder (SRBD).

The development of cardiovascular diseases (CVD) in SRBD patients is often attributed to obesity in addition to the conventional cardiac risk factors. The association between OSA and CVD is well described in the literature,
with higher incidence reported in patients with OSA than matched obese patients without OSA.7–10 There is a paucity of literature describing the cardiovascular comorbidity of patients with OHS. There are fewer data specifically addressing OHS patients’ CVD risk compared with patients with OSA alone. A few studies have suggested that pulmonary hypertension is more prevalent and more severe in patients with OHS than those with OSA alone.11–13

The mechanism of the association between SRBD and CVD is not completely understood. The hypothesis is that hypoxia and hypercapnia causes endothelial dysfunction, increased oxidative stress, sympathetic activation and high inflammatory state. These confer an additional risk to the development of CVD, including hypertension, coronary artery disease, heart failure and rhythm abnormalities.14–17

Methods
We conducted a retrospective analysis of the clinical records of patients with a formal diagnosis of OHS who were under active follow up by the Sleep Disordered Breathing Service of Auckland District Health Board as of January 2012. The study was approved by the local ethics committee (Northern X Regional Ethics Committee, Auckland, New Zealand). Patients with incomplete records and those with coexistent neuromuscular diseases were excluded from the study. The minimum dataset required was recent electrocardiogram (ECG), recent blood tests, recent pulmonary function tests and sleep study. Eight patients did not have an up-to-date echocardiogram but were included in the study.

The diagnosis of hypertension was based on documented history of high blood pressure and whether patients were actively treated with anti-hypertensive medications. Blood pressure was calculated as the average blood pressure during their most recent admission for a sleep study.

The transthoracic echocardiograms had been performed as part of the work up of the patient. Scans had been performed by a qualified echocardiogram technician in the Auckland District Health Board (ADHB) echocardiogram lab or the referring District Health Board (DHB) echocardiogram lab for those patients that were out of the ADHB catchment area. As scans had been performed over a timescale of several years and in several different departments, several different echo systems had been employed for the image acquisition. The echocardiograms were reviewed for measurements of the left ventricular ejection fraction, presence of diastolic dysfunction, ventricular wall thickness measurements, left ventricle outflow tract (LVOT) and aortic sinuses measurements and assessment of pulmonary hypertension. The ventricular dimensions were measured by the M-mode, whereas LVOT and aortic sinuses were measured by 2D echocardiography. Current medications were obtained from the electronic pharmacy records.

The clinical records of the ECG were reviewed for evidence of recurrent atrial or ventricular arrhythmias. Left ventricle hypertrophy (LVH) by voltage criteria was defined by the Sokolow–Lyon index.18 We also reviewed the results of respiratory function, renal function and the prevalence of diabetes and its current control (at the time of the sleep study) using the glycated haemoglobin (HbA1C).

Results
A total of 47 patients (23 males and 24 females) was included in our study shown in Table 1. The median age of patients was 60 years old (range 32–79). Of the patients, 42.5% had diabetes, with evidence of satisfactory glycaemic control with a mean HbA1C of 53.5 mmol/mol (reference range 20–42 mmol/mol), 65.9% had hypertension and were on long-term anti-hypertensive medications, with a mean systolic blood pressure of 127 mmHg. The mean BMI was 49 kg/m². Only three patients were classified to have stages 3 or 4 chronic kidney disease, all due to diabetic nephropathy.

Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>47</td>
</tr>
<tr>
<td>Age (IQR) (years)</td>
<td>60 (53–66)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>Female 51.1</td>
</tr>
<tr>
<td>Anti-hypertensive (%)</td>
<td>Yes 66.0</td>
</tr>
<tr>
<td>Mean SBP (mmHg) ± SD</td>
<td>127 ± 12.7</td>
</tr>
<tr>
<td>Mean BMI (kg/m²) ± SD</td>
<td>49 ± 10.3</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>Non-diabetic 57.4</td>
</tr>
<tr>
<td></td>
<td>Insulin dependent 4.3</td>
</tr>
<tr>
<td></td>
<td>Non-insulin dependent 38.3</td>
</tr>
<tr>
<td>HbA1C (mmol/mol) ± SD</td>
<td>54 ± 12.6</td>
</tr>
<tr>
<td>Arrhythmia (%)</td>
<td>No arrhythmia 63.6</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation 18.2</td>
</tr>
<tr>
<td></td>
<td>Atrial flutter 6.8</td>
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<tr>
<td></td>
<td>SVT 6.8</td>
</tr>
<tr>
<td></td>
<td>Atrial tachycardia 2.3</td>
</tr>
<tr>
<td></td>
<td>Ventricular arrhythmia 2.3</td>
</tr>
<tr>
<td>Mean FEV1 (L) ± SD</td>
<td>1.66 ± 0.73</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>73</td>
</tr>
<tr>
<td>Mean eGFR (mL/min) ± SD</td>
<td>70 ± 18.9</td>
</tr>
<tr>
<td>ECG criteria for LVH (%)</td>
<td>Yes 6.8</td>
</tr>
<tr>
<td></td>
<td>No 93.2</td>
</tr>
</tbody>
</table>

BMI, body mass index; ECG, electrocardiogram; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HBA1C, glycated haemoglobin; IQR, interquartile range; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.
The mean estimated glomerular filtration ratio (eGFR) was 71 mL/min/1.73 m². No patients were on renal replacement therapy.

The pulmonary function tests in this group revealed low spirometric lung volumes and normal forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio. All patients in our study were on nocturnal non-invasive pressure support ventilation therapy (NIV).

Poor echocardiography views were reported in 33 patients (84.6%) out of a total of 39 patients who had an echocardiogram study available (Table 2). Poor echocardiogram views were defined by the reporting physician as suitable for quantitative analysis, if measures such as M-mode had been made, but not necessarily of sufficient quality to allow accurate assessment of wall motion abnormalities. LV systolic dysfunction was found in eight patients (24%), and diastolic dysfunction was reported in 18 (60%) out of 30 patients in whom it could be assessed. Increased pulmonary artery systolic pressure as measured by the modified Bernoulli’s equation in those who had a visible tricuspid regurgitant jet was seen in 22 patients (56%) as shown in Figure 1. There was right ventricular (RV) dysfunction in 13 patients out of 25 who had good RV views on echocardiogram shown in Figure 2. With M-mode echocardiography, both the septal thickness and posterior wall thickness means were 1.3 cm (reference range 0.6–0.9 cm of both walls). The echocardiography measurements findings were discordant compared with the assessment of LVH by ECG voltage criteria. The mean intraventricular and posterior wall thickness from M-mode echocardiography was 1.3 cm, but LVH was present in only 6% of ECG.

A total of 16 patients (34%) had documented evidence of recurrent atrial or ventricular arrhythmias either during any admission to the hospital or since being diagnosed with OHS. Of those, eight patients had either paroxysmal or permanent atrial fibrillation (AF), three had recurrent atrial flutter, three had recurrent supraventricular tachycardia, one had recurrent atrial tachycardia and one had significant ventricular arrhythmias. LVH by voltage criteria was calculated by the Sokolow–Lyon index in the most recent ECG, and only three patients (6%) had ECG evidence of LVH.

Table 2  Echocardiogram findings

<table>
<thead>
<tr>
<th>Echocardiogram quality (%)</th>
<th>Good quality</th>
<th>12.8</th>
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<tbody>
<tr>
<td></td>
<td>Poor quality</td>
<td>70.2</td>
</tr>
<tr>
<td></td>
<td>Not done</td>
<td>17.0</td>
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</table>

<table>
<thead>
<tr>
<th>Left ventricular ejection fraction (%)</th>
<th>Not assessed</th>
<th>17.9</th>
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<tbody>
<tr>
<td></td>
<td>Normal (EF &gt; 55%)</td>
<td>61.5</td>
</tr>
<tr>
<td></td>
<td>Mild dysfunction</td>
<td>15.4</td>
</tr>
<tr>
<td></td>
<td>Moderate dysfunction</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>Severe dysfunction</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diastolic dysfunction (%)</th>
<th>Yes</th>
<th>60.0</th>
</tr>
</thead>
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<tr>
<td></td>
<td>No</td>
<td>40.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean LVOT ± SD (cm)</th>
<th>2.5 ± 0.19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Ao sinuses diameter ± SD (cm)</td>
<td>3.7 ± 0.41</td>
</tr>
<tr>
<td>Septal wall thickness ± SD (cm)</td>
<td>1.3 ± 0.20</td>
</tr>
<tr>
<td>Posterior Wall thickness ± SD (cm)</td>
<td>1.3 ± 0.16</td>
</tr>
<tr>
<td>LV end diastolic diameter ± SD (cm)</td>
<td>5.6 ± 0.74</td>
</tr>
<tr>
<td>LV end systolic diameter ± SD (cm)</td>
<td>4 ± 0.67</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Right ventricular systolic function (%)</th>
<th>Normal</th>
<th>36.7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild impairment</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Moderate impairment</td>
<td>40.0</td>
</tr>
<tr>
<td></td>
<td>Severe impairment</td>
<td>10.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pulmonary HTN</th>
<th>&lt;30 mmHg</th>
<th>12.0%</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>30–50 mmHg</td>
<td>36.0%</td>
</tr>
<tr>
<td></td>
<td>&gt;50 mmHg</td>
<td>52.0%</td>
</tr>
</tbody>
</table>

Ao, aortic; HTN, hypertension; LVOT, left ventricle outflow tract.

Figure 1  Higher incidence of pulmonary hypertension and diastolic dysfunction in patients with obesity hypoventilation syndrome.

Figure 2  Presence and severity of right ventricular dysfunction.

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Discussion

Obesity is a growing clinical problem. According to New Zealand Ministry of Health statistics, it is estimated that 28% of the adult NZ population were classified as obese (BMI >30) in 2011/2012. This rate has increased from 26% since 2006/2007. Obesity affected all age groups of the adult population with an overall equal male to female ratio. There was a higher incidence of obesity in the Maori (44%) and Pacific (62%) ethnic groups which has not changed since 2006/2007.

In the Wisconsin sleep cohort study, it was estimated that OSA has a prevalence of 2–9% of the general adult population when OSA was defined as an Apnoea Hypopnoea Index (AHI) of more than five in addition to the presence of symptoms. The population prevalence of OHS is not as well described in the literature, although some estimates showed that approximately 10–20% of patients presenting to outpatient sleep clinics have evidence of OHS. Overall, both OSA and OHS are believed to be under-diagnosed, with most patients seeking medical attention only once they have significant symptoms.

Obese patients with SRBD often have a stronger association with CVD than matched control obese subjects without SRBD, although proving causality remains elusive, the balance of evidence is beginning to support a causal relationship at least with stroke. There are not many data in the literature about OHS and its association with CVD specifically. It is reasonable to hypothesise that hypercapnia that increases severity of nocturnal hypoxia and the more severe sleep apnoea associated with OHS could confer extra risk factors. However, to what degree OHS further increases the well recognised association of increased cardiovascular risk in OSA is unknown.

There are various therapies for sleep disordered breathing, including continuous positive airway pressure (CPAP) for OSA or OSA associated with OHS, and NIV, usually bi-level positive airway pressure (BIPAP) for OHS. Treatment of OSA with CPAP was shown to have benefits beyond symptomatic relief of symptoms of sleep apnoea. In one study, treatment of coexisting OSA by CPAP in patients with heart failure reduced systolic blood pressure and improved left ventricular function; however, to date no prospective studies have demonstrated improved clinical outcomes. Meta-analysis of the effect of effective CPAP treatment in patients with moderate to severe OSA leads to a modest decrease in daytime blood pressure (systolic blood pressure (SBP) −2.58 mmHg (95% CI −3.57 to −1.59); diastolic blood pressure (DBP) −2.01 mmHg (95% CI −2.84 to −1.18)). In our cohort, the blood pressure control as measured by the average blood pressure during their most recent elective admission to the hospital for sleep studies was adequate with a mean SBP of 127 mmHg.

The methods of cardiac function assessment are somewhat limited in our study due to poor images quality obtained by echocardiography. This is a common limitation of echocardiogram studies in general in obese patients due to mechanical factors. Unfortunately other methods of cardiac assessment are usually not practical, too expensive or too invasive, such as cardiac MRI or LV grams during cardiac catheterisation respectively in this group of patients.

Even with those limitations the findings in our cohort suggest a high prevalence of LV systolic and diastolic impairment. These could be even under-estimated due to poor image quality due to high BMI. The prevalence of echocardiographic pulmonary hypertension was also high despite this limitation, and two-thirds of those with pulmonary hypertension had severely elevated pressures (PASP >50 mmHg + RA mean pressure) as assessed by the modified Bernoulli’s equation. Pulmonary hypertension is common in this group of patients. The cause of pulmonary hypertension can be due to the chronic hypoxia, left heart disease or obesity. No patient had undergone right heart catheterisation (RHC) to assess pulmonary artery and pulmonary artery wedge pressure in this study. However, from the transthoracic echocardiogram data, 24% of patients had LV systolic dysfunction and 60% had diastolic dysfunction.

Morbid obesity on its own can produce alterations to the baseline ECG patterns compared with normal controls. In our study we only focused on the diagnosis of LVH by voltage criteria. Despite that septal thickness and posterior wall thickness were both markedly higher in our cohort than the normal reference range, LVH by voltage criteria was only positive in 6% of patients. Again the mechanical factors seen in obese patients due to the relatively long distance between the ECG electrodes and the heart should alert clinicians that there are limitations of ECG in the morbidly obese patient such as that seen in LVH, T wave flattening and R wave progression on chest leads.

The association between OSA and AF was first described by Apo et al. in 2004. It was noted that AF association with OSA was strikingly more prevalent in OSA patients than other high-risk patients with multiple cardiac risk factors. We found in our study that at least 17% of OHS patients had documented evidence of either paroxysmal or permanent AF. We also found that more patients had evidence of other recurrent arrhythmias, including atrial tachycardia, supraventricular tachycardia and ventricular tachycardia.

The studies that showed association between SRBD and cardiovascular diseases were mainly studying a
cohort of OSA patients. In our study we have focused on OHS patients, all of whom have underlying OSA as well. However, in some studies that there is no clear definition whether patient selection included those with a coexisting OSA and OHS. In fact some were describing hypercapnia in the discussion of disease mechanism, which is a feature of OHS, and much rarer in isolated OSA though can be seen where apnoeas are so frequent and prolonged there is insufficient time between apnoeas to blow off CO₂ during the night.

**Limitations**

There are several limitations to this study. First, as the study is a retrospective analysis of patients over several years, the echocardiogram data are limited. Earlier, patients were scanned using older echocardiogram systems with the associated limits on image quality. Newer systems have improvements such as tissue harmonic imaging. Also, ultrasound-based contrast was not available in our unit until relatively recently. Guidelines for the accurate assessment of especially the right heart have also changed over time, and many of the older datasets do not contain measures, such as tricuspid annular plane systolic excursion (TAPSE). Echocardiography in this group of patients is notoriously difficult. A previous study has shown that measures, such as pulmonary pressures, are difficult to obtain even with the use of ultrasound-based contrast.

Twelve out of the 47 patients are from a different DHB and therefore were only assessed once in our institution with ongoing follow up at their local hospital. Only four of the 47 patients have a documented second transthoracic scan. It has not been the policy of the department to perform RHC in these patients.

Further studies are needed to determine specific cardiovascular risks of OHS patients that might need a more urgent investigation and more aggressive management. This study is limited by its small size. However, it does show that patients with OHS receiving NIV have a higher prevalence of CVD.

**Conclusion**

Patients with OHS have a high prevalence of CVD, as demonstrated in the present study. The hypoventilation and other pathophysiological alterations during sleep appear to be an additional risk factor for the development of CVD in addition to the other conventional cardiac risk factors. Identifying these issues and providing specific treatment may play a role in decreasing the impact and costs associated with CVD. Larger prospective studies are needed to confirm the significance of these issues.

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Acute effects of different degrees of ultra-endurance exercise on systemic inflammatory responses

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Key words
physical exercise, ironman, iron metabolism, osteocalcin, irisin.

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Abstract

Background: Intense physical stress might promote inflammatory responses, whereas a regular physical exercise has positive influence. Little is known on the acute metabolic and inflammatory responses to different levels of strenuous exercise in trained athletes.

Aim: To compare the short-term effect of two different ultra-endurance competitions on the inflammatory profile in male triathletes.

Methods: We studied 14 Ironman (IR) and 13 Half Ironman (HIR) before and after their own specific race. We assessed body composition and measured blood cells, lipids, iron metabolism and plasma levels of some acute-phase cytokines and inflammatory markers.

Results: After the race, IR showed reduced total body water and fat-free mass, not related with the duration of exercise, and increased white cells and platelets; high-density lipoprotein levels also increased. IR, but not HIR, showed reduced iron levels, increased ferritin and transferrin, reduced % saturated transferrin. HIR showed higher basal interleukin (IL)-6, tumour necrosis factor (TNF)-α, IL-10, IL-1β than IR; however, the post-performance rise was greater in IR. Irisin increased only in HIR and osteocalcin decreased in IR. In the whole study group, delta of white blood cells was directly related with delta of monocyte chemoattractant protein 1, and Δ ferritin was inversely related with Δosteocalcin.

Conclusions: A single ultra-endurance competition induces an inflammatory response depending on the duration of physical effort, with increased acute-phase cytokines, and an altered iron metabolism. Irisin, whose biological meaning is still uncertain, seems to be associated with acute variations of some metabolic parameters.

Introduction

A sedentary lifestyle is considered an independent risk factor for the development of atherosclerosis and coronary heart disease (CHD), and the most important scientific societies unequivocally advise an increase in physical activity in the prevention and treatment of CHD; however, mechanisms that underlie the effectiveness of exercise in preventing or treating CHD have not been completely established.¹ In the attempt to clarify better this complex issue, the link between exercise and inflammation has recently received special attention.² Acute bouts of exercise result in a transient increase in acute-phase reactants and cytokines, related to the amount of exercise and muscle injury;³ on the other hand, regular activity has been repeatedly associated with a chronic anti-inflammatory effect having a potential positive influence on the vasculature.⁴ Beside weight reduction, likely the main determinant of the reduced cardiovascular risk exerted by physical activity, other beneficial effects of physical exercise include the modulation of the activation of specific cytokine cascades, the signalling pathways associated with insulin resistance and the activity and reactivity of the vascular endothelium;⁵ however, mechanisms underlying such effects are not fully clarified.

A competition of Ironman (IR) triathletes is an ultra-endurance event in which athletes perform to 3.8-km swim, 180-km cycling and 42.197-km running without interruption; competition on the middle distances is defined as the Half Ironman (HIR) race. This extreme sport activity requires a meticulous and demanding training, and exposes athletes to a strenuous physical stress...
able to influence their physiology radically, including pathologic structural remodelling of the heart and large arteries, and to cause significant changes in biochemical parameters.\textsuperscript{5} Chronic endurance training leads to improvements in glucose metabolism and lipoprotein profile; regarding changes that acutely occur immediately after strenuous exercise, a rise in markers of acute-phase inflammation has been reported,\textsuperscript{7} whereas little is known on the inflammatory molecules more strictly related to the development of atherosclerotic process and to an increased cardiovascular risk, like monocyte chemoattractant protein-1 (MCP-1) and high-sensitivity C-reactive protein (hsCRP),\textsuperscript{6} or to the metabolic adaptation to physical exercise, like irisin, whose expression, enhanced during exercise, is able to stimulate the browning of white fat tissue and uncoupling protein-1 expression, with an improvement in glucose homeostasis.\textsuperscript{7}

In these triathletes, information on the effects of an acute bout of exercise on iron metabolism are also lacking, making the relationship between iron trafficking and pro-inflammatory activation of macrophages even more complex.\textsuperscript{10} Iron homeostasis may also regulate bone metabolism;\textsuperscript{11,12} in this view, bone metabolism has been quite largely studied after acute exercise,\textsuperscript{13,14} but few studies have evaluated the performance of bone formation markers in elite athletes, characterised by a higher bone turnover,\textsuperscript{15} linking them to iron metabolism. To contribute in clarifying this complex issue, we planned a study aimed at evaluating how an IR or an HIR race might affect the inflammatory profile in amateur athletes, paying special attention to cytokines involved in the modulation of acute-phase responses and bone remodelling.

\section*{Methods}

\subsection*{Participants}

Study subjects were recruited on a volunteer basis among male participants of Elbaman, an IR and HIR triathlon competition, which takes place in the Elba Island, Italy, in the early autumn. The protocol was approved by the Ethical Committee of Valle d’Aosta region (n. 65943; 13 July 2013) and all the volunteers signed an informed consent according to the Declaration of Helsinki. Exclusion criteria were the use of any medication, antioxidant or related supplements and febrile illness in 7 days preceding the study. The triathletes (all males, well trained, non-smokers, free of acute and chronic illnesses) did not exercise for 24 h preceding the race.

\subsection*{Main outcome measurements}

The day before the race, a brief medical history was collected in all athletes; weight and height, blood pressure values, heart rate and saturation (by pulse-oximeter Tuff-Sat, Datex-Ohmeda, GE Healthcare Europe, Milan, Italy) were registered, and body composition was assessed by bioelectrical impedance analysis using a TANITA TBF-300A Body Composition Analyzer (Tanita Corporation, Arlington Heights, IL, USA), on the basis of standardised mathematical formulae. The following parameters were measured: body mass index (BMI), fat mass (FM), fat-free mass (FFM), total body water (TBW). A venous blood sample was drawn from an antecubital vein, collected into vacutainers and centrifuged at 1500 r.p.m. for 10 min at 4°C; a mobile testing laboratory was used at the race to ensure appropriate collection, separation and storage of samples.

On the day of the race, the ambient temperature was 23.2°C. The mean duration of exercise was 12:48:21 ± 1:14:18 h for IR and 6:14:43 ± 0:37:25 h for HIR. Athletes were allowed to eat and drink ad libitum during the race, and nutrition was provided during the cycling and running courses by the organisers. At the end, they were placed in thermal blankets, and all tests were repeated within 15 min; after that, athletes were fed.

Biochemical parameters and a complete evaluation of iron metabolism were measured by standard methods; hsCRP was determined by nephelometric analysis. The acute-phase cytokines tumour necrosis factor (TNF)-α (an adipokine involved in systemic inflammation), interleukin (IL)-1β (involved in the proliferation, differentiation and apoptosis of cells, and associated with septic shock, and wound healing), IL-6 (able to stimulate acute-phase protein synthesis, as well as the production of neutrophils in the bone marrow), and IL-10 (showing prevailing anti-inflammatory effects), the chemotactic factor MCP-1, irisin and osteocalcin (a marker of bone mineral density) were assessed by enzyme-linked immunosorbent assay according to the manufacturer’s instructions (Quantikines kits, R&D Systems, Wiesbaden, Germany; intra-assay coefficients of variation were 3.1, 5.4, 7.4, 3.6, 4.9, 6.0 and 3.1% respectively). There were 40 athletes who participated in the race; 14 athletes competing in the IR distance and 13 in the HIR distance completed the race and were therefore selected for data collection.

Statistical analysis

Data are expressed as mean ± standard deviation. Group comparisons were performed using the non-parametric Mann–Whitney \textit{U}-test or the unpaired \textit{t}-test, for variables with non-normal or normal distribution, respectively, and \textit{χ}^2 for categorical variables. Variations of the different parameters after the race respect to baseline were evaluated by analysis of variance for repeated observations, correcting with post-hoc Bonferroni test.
Table 2 Biochemical parameters at baseline and after exercise in Ironman and Half Ironman

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-exercise</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ironman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>70.2 ± 5.5</td>
<td>68.2 ± 5.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.90 ± 1.42</td>
<td>22.34 ± 1.31</td>
<td>ns</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>65.1 ± 5.6</td>
<td>62.7 ± 5.8</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>5.1 ± 2.5</td>
<td>5.5 ± 2.0</td>
<td>ns</td>
</tr>
<tr>
<td>TBW (kg)</td>
<td>47.6 ± 4.1</td>
<td>45.9 ± 3.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Half Ironman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>71.2 ± 7.4</td>
<td>69.5 ± 7.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.40 ± 1.97</td>
<td>22.86 ± 2.01</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>66.1 ± 5.9</td>
<td>64.1 ± 6.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>5.3 ± 2.7</td>
<td>5.5 ± 2.4</td>
<td>ns</td>
</tr>
<tr>
<td>TBW (kg)</td>
<td>48.2 ± 4.3</td>
<td>47.0 ± 4.4</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Data are reported as mean ± standard deviation. BUN, blood urea nitrogen; HCT, haematocrit; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCV, mean cellular volume; PLT, platelets; RBC, red blood cells; WBC, white blood cells.

Relationships between variables were assessed using Spearman’s correlation analysis and multiple linear regression analysis. The statistical significance was determined on a probability level of <0.05. Data were analysed with StatView for Windows (SAS Institute, San Francisco, CA, USA).

Results

Effect of the two different competitions on body composition

The two groups did not differ in age or clinical characteristics (Table S1). At the end of the test, with the limitations of the used techniques (the study was carried out directly on the race field), the significant reduction of TBW content and FFM observed in all the athletes was of greater extent in IR than in HIR (Table 1); this translated in a reduced BMI only in IR, despite the reduction in bodyweight being significant in both groups. No correlation was found between duration of exercise and Δ (exercise-rest) in bodyweight, FFM and TBW content.

Effect of the two different competitions on biochemical parameters

At baseline, the main biochemical values were similar between IR and HIR, with no clinically significant difference in blood glucose, lipid profile, iron metabolism pattern and blood count parameters (Table 2). In both groups, the physical performance induced an almost threefold rise in white blood cells despite no variation in haematocrit value; change in platelets count was not relevant. Moreover, IR, but not HIR, was characterised by significant variations of the iron pattern, with reduced serum iron levels, increased ferritin and transferrin and clearly lower percent of transferrin saturation.

Concerning the lipid pattern, increased HDL-cholesterol levels were observed after the race; interestingly, the increase was twofold higher in IR than in HIR (+25% vs +13.3%), and this was coupled with a significant reduction of low-density lipoprotein (LDL) cholesterol. The acute exercise did not significantly affect triglycerides (Table 2). In the whole study population, the duration of exercise was directly correlated with

Table 2 Biochemical parameters at baseline and after exercise in Ironman and Half Ironman

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-exercise</th>
<th>Half Ironman</th>
<th>Post-exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>4.28 ± 0.72</td>
<td>4.22 ± 0.78</td>
<td>4.44 ± 0.28</td>
<td>5.56 ± 1.17*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.50 ± 0.88</td>
<td>5.35 ± 0.67</td>
<td>4.96 ± 0.49</td>
<td>5.22 ± 0.65*</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.83 ± 0.39</td>
<td>2.30 ± 0.28*</td>
<td>1.63 ± 0.31</td>
<td>1.83 ± 0.36*</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.02 ± 0.07</td>
<td>2.66 ± 0.52*</td>
<td>2.76 ± 0.52</td>
<td>2.82 ± 0.59</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.34 ± 0.45</td>
<td>1.20 ± 0.33</td>
<td>1.28 ± 0.77</td>
<td>1.28 ± 0.42</td>
</tr>
<tr>
<td>Osmolarity (mOsm/L)</td>
<td>298 ± 4</td>
<td>308 ± 6*</td>
<td>297 ± 5</td>
<td>311 ± 8*</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>7.2 ± 1.6</td>
<td>11.9 ± 2.6*</td>
<td>6.8 ± 1.1</td>
<td>8.6 ± 1.1*</td>
</tr>
<tr>
<td>Iron (μg/dL)</td>
<td>112 ± 35</td>
<td>49 ± 14*</td>
<td>106 ± 30</td>
<td>97 ± 33</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>126 ± 78</td>
<td>150 ± 90*</td>
<td>95 ± 38</td>
<td>101 ± 35</td>
</tr>
<tr>
<td>Transferrin (mg/dL)</td>
<td>280 ± 42</td>
<td>301 ± 52*</td>
<td>280 ± 20</td>
<td>309 ± 38*</td>
</tr>
<tr>
<td>WBC (10³/μL)</td>
<td>5.23 ± 0.83</td>
<td>16.85 ± 2.37</td>
<td>6.45 ± 3.29</td>
<td>14.27 ± 3.19*</td>
</tr>
<tr>
<td>RBC (10⁶/μL)</td>
<td>4.69 ± 0.48</td>
<td>4.87 ± 0.37</td>
<td>4.91 ± 0.30</td>
<td>5.00 ± 0.44</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>14.2 ± 0.6</td>
<td>14.4 ± 0.8</td>
<td>14.9 ± 0.7**</td>
<td>15.3 ± 1.0*</td>
</tr>
<tr>
<td>HCT (%)</td>
<td>42.6 ± 2.1</td>
<td>42.2 ± 2.5</td>
<td>43.9 ± 1.8</td>
<td>45.0 ± 2.5*</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>90.9 ± 2.9</td>
<td>88.9 ± 3.0*</td>
<td>90.3 ± 3.7</td>
<td>89.3 ± 3.8*</td>
</tr>
<tr>
<td>PLT (10⁹/μL)</td>
<td>228 ± 43</td>
<td>274 ± 37*</td>
<td>201 ± 35</td>
<td>229 ± 19</td>
</tr>
</tbody>
</table>

*P < 0.05 versus baseline; **P < 0.05 versus Ironman. Data are reported as mean ± standard deviation. BUN, blood urea nitrogen; HCT, haematocrit; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MCV, mean cellular volume; PLT, platelets; RBC, red blood cells; WBC, white blood cells.
Table 3 Plasma levels of inflammatory markers in Ironman and Half Ironman athletes before and immediately after their respective race

<table>
<thead>
<tr>
<th></th>
<th>Ironman</th>
<th>Half Ironman</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-exercise</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>1.4 ± 0.4</td>
<td>3.1 ± 1.0*</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>10.9 ± 4.3</td>
<td>12.7 ± 3.1</td>
</tr>
<tr>
<td>IL-1β (pg/mL)</td>
<td>20.9 ± 17.1</td>
<td>25.3 ± 21.7</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>4.2 ± 2.7</td>
<td>18.9 ± 13.1*</td>
</tr>
<tr>
<td>IL-10 (pg/mL)</td>
<td>11.5 ± 6.6</td>
<td>63.5 ± 65.9*</td>
</tr>
<tr>
<td>MCP-1 (pg/mL)</td>
<td>337 ± 165</td>
<td>1116 ± 598*</td>
</tr>
<tr>
<td>Irisin (μg/mL)</td>
<td>0.9 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>Osteocalcin (μg/mL)</td>
<td>5.0 ± 2.8</td>
<td>3.7 ± 2.0*</td>
</tr>
<tr>
<td>Bone alkaline phosphatase (μg/L)</td>
<td>11 ± 2</td>
<td>11 ± 3</td>
</tr>
</tbody>
</table>

*P < 0.05 versus baseline; **P < 0.05 versus Ironman. Data are reported as mean ± standard deviation. IL, interleukin; hsCRP, high-sensitivity C-reactive protein; MCP, monocyte chemoattractant protein; TNF, tumour necrosis factor.

ΔHDL-cholesterol ($R^2 = 0.206, P = 0.039$) and inversely with ΔLDL cholesterol ($R^2 = 0.15, P = 0.044$).

**Effect of the two different competitions on inflammatory parameters**

Table 3 shows circulating concentrations of inflammatory markers in IR and HIR before and after the respective race. Even in the presence of a relevant variability, HIR were somehow more ‘inflamed’ at baseline, showing higher levels of TNF-α and IL-6 respect to IR, whereas MCP-1 was lower. After acute exercise, a significant increase in levels of Hs-CRP, IL-6, IL-10 and MCP-1 was observed in both groups, with more marked increases in IR when compared with baseline levels. TNF-α did not significantly vary after the race, irisin increased only in HIR, as well as IL-1β (even though not significantly), whereas osteocalcin was reduced in IR. Alkaline phosphatase was similar in IR and HIR and did not significantly vary after the race.

In the whole study group, an inverse relationship emerged between Δferritin and Δosteocalcin ($R^2 = 0.276, P = 0.059$).

In the whole study population, the ΔWBC significantly correlated with ΔMCP-1 ($R^2 = 0.179, P = 0.05$). A model of multiple regression analysis including all the inflammatory cytokines, after correction for age and FFM, showed that besides MCP-1, basal irisin levels were also the main determinants of ΔWBC ($R^2 = 0.747, P = 0.018$ for MCP-1 and 0.0012 for irisin).

**Discussion**

This study offers a detailed picture of the effect of specific competitions on some inflammatory parameters in ultra-endurance triathletes, allowing a comparison between two races characterised by a different level of intensity. The metabolic pattern of such athletes is characterised by relevant variations of the body composition, and the measurement of body impedance provides reliable information about the FM and FFM loss, allowing an estimation of tissue catabolism during an ultra-endurance exercise. Variations of fat-free mass and bodyweight are fully expected after such level of physical stress; our results are comparable, even quantitatively, with those registered with more sophisticated techniques like dual-energy X-ray absorptiometry and quantitative computed tomography; the difference between IR and HIR is likely due to the greater intensity of the effort and the concomitant lesser degree of integration of liquids and food during stress. Despite the significant reduction in TBW shown by all the athletes, we confirm no variation in haemoglobin and haematocrit; as expected, plasma osmolarity slightly increased after the race.

Regarding lipid metabolism, it is known that HDL cholesterol concentrations increase with regular exercise, therefore contributing to a lower risk of CHD in physically active individuals compared with sedentary subjects. Relevant changes in the lipid profile, including a rise in HDL levels, immediately following the physical performance were documented in IR several years ago; however, the clinical advantage of such observation has been more recently re-evaluated, in the light of an inconvenient increased lipid peroxidation and, ultimately, oxidative stress. It should be emphasised that our study population was characterised at baseline by higher HDL-cholesterol values than those normally observed in age and gender-matched individuals not exposed to a continuous training programme for endurance-oriented activities, whose influence is confirmed by the relation, even in the acute setting, with the duration of physical performance.

The inflammatory pattern shown by IR and HIR before and immediately after the race is very complex. The increased WBC count has been previously described and attributed to an increased cell mobilisation in response to exercise-induced muscle damage, with activation of the alternative complement pathway; however, the free fluid intake during the race made this effect neutral on haematocrit value.

We report here for the first time a significant rise in MCP-1 levels in both groups, and a strict relationship between baseline MCP-1 title and ΔWBC, thus offering...
an alternative mechanism through which polymorphonuclear leucocytes can be mobilised. The baseline haemoglobin value in the low–normal range, already described in these athletes, might be due to a chronic iron deficiency. However, a complete view on how a physical performance can acutely influence iron metabolism in IR is shown here; results suggest a causative relationship linking the pro-inflammatory status induced by such intensive physical effort, the subsequent iron consumption and the changes in serum ferritin (a direct mediator of the immune system). In this view, the relevant increment of IL-6 levels is interesting, and it was recently found to be able to rise hepcidin, a negative regulator of iron status.

A state of quick subclinical inflammation, sustained by the physical performance, is confirmed by the rise of hsCRP, which occurs faster than that observed by other authors. Mechanical and metabolic stress are responsible for the exercise-induced muscle damage, whose main consequence is the rapid increase in plasma IL-6 concentration; however, in a global metabolic evaluation, this phenomenon might not necessarily be negative, in light of the recent description of a protective effect exerted by IL-6 on β-cell function and insulin secretion, through a reduced glucagon and an increased glucagon-like peptide-1 production. The already described rise in IL-10 levels, with a probable role of counter-regulatory anti-inflammatory cytokine, capable to attenuate the inflammatory and immune response to prevent over-shooting inflammation, was unable, in our study population, to suppress or reduce TNF-α, whose basal levels, even higher with respect to the general population, are similar to those already described in athletes practising strenuous exercise. We also report here some novel observations: as mentioned above, MCP-1 increases in both IR and HIR after the race. This trend is in agreement with a recent report obtained in duathlon male athletes.

The present data do not firmly confirm the relationship between the amount of exercise and circulating levels of irisin; even though IR, more trained than HIR, showed slightly higher basal irisin, the race did not acutely induce any appreciable variation. Such data, although coming from an observational study, suggest, as a very preliminary observation partially agreeing with another recent report, that ultra-endurance exercise, even transiently impairing muscle integrity, does not influence circulating levels of this myokine.

In contrast with a previous report, we show here that levels of osteocalcin, a marker of bone remodelling, declined in IR after a full-length ultra-endurance competition, but not in HIR. A possible explanation for this unexpected result in IR is the inverse correlation recently found between ferritin and osteocalcin, which is confirmed in our study even after the acute competition, with an intriguing dowregulatory effect of iron load on osteocalcin synthesis that recalls the recently emerged extra-skeletal effects of osteocalcin, with hormonal influence on energy balance and insulin metabolism.

Limitations of the present study include a relatively small number of subjects, a lack of precise control in water intake or feeding during the race and the lack of a further blood sampling after a more prolonged recovery, beside that obtained immediately after the race.

Conclusion
A single ultra-endurance competition induces an inflammatory response depending on the duration of physical effort, with increased acute-phase cytokines, and an altered iron metabolism. Follow-up studies strictly monitoring IR athletes during their adult and mature age would clarify whether such strong physical training would be really advantageous in reducing cardiovascular risk, overcoming the effect exerted by the inflammatory status occurring after these strenuous performances.

Acknowledgements
We thank all the volunteers participating in this study.

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Supporting Information

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

**Table S1** Clinical characteristics of ultra-endurance athletes.
Trends in the incidence of intensive care unit invasive mechanical ventilation and subsequent 2-year survival in very elderly New Zealanders

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Key words
intensive care units, respiration, artificial, aged 80 and over, mortality, outcome assessment.

Abstract
Background: The number of elderly in the general population is growing. There are therefore implications for the provision of intensive care unit (ICU) care to elderly patients.

Aim: Our aim was to determine the incidence of ICU invasive mechanical ventilation (IMV), long-term outcomes of patients treated with IMV, and trends in these variables over a 10-year period in New Zealand, with a focus on very elderly patients (aged 80 years and over).

Methods: Analysis of New Zealand public hospital discharge data from July 1999 to June 2010, with linked long-term mortality data. Transfers or readmissions to different hospitals were linked using a national unique patient identifier.

Results: There were 58,003 patients treated with IMV in a New Zealand ICU. Of these patients, 6.6% were very elderly. Population rates of ICU IMV declined or were static over all age groups. The 2-year mortality rate ranged from 15% in patients aged 16–39 years to 52% in the very elderly. The 2-year mortality rates for the very elderly were highest for acute medical patients (78%), followed by acute surgical admissions (46%) and elective admissions (35%). The 2-year mortality rate for all patients declined over the study period, and declined or was static for all age groups and admission types. In the very elderly, the standardised mortality ratio of patients surviving at 1 year who survived their second year after admission, compared with the age-matched general population, was lower than all other age groups.

Conclusion: For very elderly patients over the period 1999–2009, the population rate of IMV was static and 2-year mortality declined.

Introduction

The number of very elderly people in New Zealand is increasing,1 consistent with global trends of a 3.8% per annum increase.2 This is anticipated to impact on the number of patients in this age group treated with invasive mechanical ventilation (IMV) in intensive care units (ICU).

Older people more often declined ICU treatment than younger patients.3 The very elderly who are admitted to the ICU have fewer comorbidities than elderly ICU patients. Further, older patients have a different case mix from younger patients, with fewer cases of acute asthma, ketoacidosis and drug overdose, and more cases of cardiogenic shock and exacerbations of chronic obstructive pulmonary disease.4,5 Treatment intensity once admitted to an ICU is lower for the very elderly, with lower rates of IMV,4 renal replacement and tracheostomy.6,7

Given this variability in presentation, admission and treatment, it is not surprising that the proportion of very elderly people treated in ICU varies considerably across countries, independent of illness severity and comorbidities.3

In Australia and New Zealand, the number of very elderly patients admitted to ICU increased at 5.6% per annum in an analysis of 120,123 ICU admissions.8

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However, little is known about trends in the absolute number and proportion of very elderly patients treated with IMV and, in particular, their long-term survival following hospital discharge.

The true value of intensive care should be determined by long-term rather than short-term survival. A large Australian retrospective cohort study found increasing age, among other factors, was negatively associated with survival at 1, 3, 5, 10 and 15 years of follow up. However, the impact of age on mortality independent of associated comorbidities has varied in a number of generally small studies.

Against this background, this study aimed to address two questions. First, what trends are evident in the number of very elderly New Zealanders admitted to an ICU and treated with IMV, compared with increases in the general population? Second, what trends are evident in the longer-term outcomes of very elderly ICU IMV patients compared with younger IMV patients, as measured by in-hospital, 1- and 2-year mortality rates?

Methods

Data were obtained from the New Zealand Ministry of Health (MoH) National Minimum Data Set (NMDS). This is an administrative database of all inpatient discharges from all public hospitals. Since July 1999, these data have included the number of hours a patient was treated with IMV under the care of an intensive care team. No inpatient severity data are contained within this data set nor is the length of ICU stay.

Each patient in New Zealand has a unique patient identifier, the National Health Index (NHI) number, included in each NMDS admission record. Different admissions by the same patient at any hospital were therefore able to be linked.

The NMDS records the date of death if the patient has died either during the admission or at any time subsequently. The date of death is obtained from hospital admission data for inpatient deaths and by NHI linkage with the New Zealand death register maintained by the Department of Internal Affairs for post-discharge deaths.

Data were extracted for every inpatient event in the NMDS, for patients discharged over the 11 years from July 1999 to June 2010, where ‘ventilation hours’ was greater than 0 and the patient was 16 years or older. Data included demographics, dates of hospital admission and discharge, International Classification of Diseases version 10 (ICD 10) diagnostic and procedure codes, and date of death if present. Consecutive admissions to different hospitals by the same patient were assumed to be transfers and were merged to form one admission.

Incidence of IMV data are reported to June 2010. Mortality data were derived using date of death if the patient died before June 2011. The 2-year mortality data are therefore reported for admissions up to June 2009.

Mortality is described over three time periods: inhospital mortality, mortality from discharge to 1-year post-admission (termed ‘first-year mortality’) and from 1-year post-admission to 2-year post-admission (termed ‘second-year mortality’).

Admissions were categorised as acute medical, acute surgical or elective using the NMDS admission definitions of acute admission (on the day), arranged (admission planned one to 6 days in advance) or elective (planned more than 6 days in advance). Patients were considered ‘acute’ in this study if they were an acute or arranged admission.

Acute patients were classified as medical or surgical on the basis of the Diagnostic Related Group (DRG) version 3.1 partition code. A patient is thus classified as surgical on the basis of a surgical diagnosis – irrespective of whether an operation was performed. For patients ventilated longer than 96 h, the DRG classification does not discriminate between medical and surgical admissions. These patients were manually classified on the basis of their principal diagnosis, reported surgical procedures and whether the discharge specialty was a medical or surgical discipline.

Rates of IMV were compared with Poisson regression using the genmod procedure in SAS (SAS Institute Inc., Cary, NC, USA) with adjustment for 5-year age bands within each broader age group. Proportions were compared with Chi-squared tests. Length of stay data were compared with a Kruskal–Wallis test. Trends in the 2-year mortality rate were estimated with generalised linear models with a binomial distribution and a log link.

Population data were provided by the Ministry of Health. Life-expectancy data of the general population were obtained from Statistics New Zealand and are derived from New Zealand’s 5-yearly census. Life-expectancy data are taken from the 2000–2002 and 2005–2007 life tables for estimates of 1-year survival at each year of age, extrapolated between them, and using the fitted linear trend from the abridged life tables for later years (which only categorise life expectancy in 5-year cohorts).

The New Zealand Central Region Ethics Committee confirmed that ethical approval was not required for this observational study.

Results

Demographics of ventilated patients

There were 58 003 admissions treated with IMV in a New Zealand public hospital ICU between June 1999 and July
2010 (Table 1). Those aged 40–64 years were the largest group (39.3%), followed by patients aged 65–79 years (35.3%). The very elderly were a small proportion (6.6%).

There was no statistically significant change in the total number of patients treated with IMV per year over the 10-year period of the study (0.6% per annum, 95% confidence interval (CI) −0.9–2.0; Table 2). Numbers treated with IMV in each age group were similarly static, apart from growth in the 40- to 64-year-olds group (1.6% per annum, 95% CI 0.1–3.1).

Over this same period, there was a 1.7% per annum growth in the general New Zealand population, with the number of very elderly growing by 3.5% per annum.

There was a decrease in the population rate of IMV in total (1.4% per annum, 95% CI −1.8 to −0.9), and for patients aged 40–64 and 65–79 years, but not in the very elderly (−1.1% per annum 95% CI −2.9 to 0.8).

### Mortality rate of ventilated patients

Inhospital mortality, first-year mortality and second-year mortality rates all increased with age ($P < 0.0001$, Chi-squared tests for trend; Fig. 1). There were significant differences in the mortality distributions between the age groups ($P < 0.0001$ Chi-squared test). A higher proportion of 16- to 39-year-old and over 80-year-old deaths occurred in hospital (78% and 74% vs 70% for 40- to 79-year-old patients).

### Table 1 Demographics of ventilated patients

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>16–39</th>
<th>40–64</th>
<th>65–79</th>
<th>80+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10 874</td>
<td>22 821</td>
<td>20 482</td>
<td>3826</td>
<td>58 003</td>
</tr>
<tr>
<td>Population rate of IMV per 10 000 population per year for 1999–2010 (95% CI)*</td>
<td>6.9 (6.8–7.0)</td>
<td>16.6 (16.4–16.8)</td>
<td>50.6 (49.9–51.3)</td>
<td>28.0 (27.1–28.9)</td>
<td>16.6 (16.5–16.7)</td>
</tr>
<tr>
<td>% males (95% CI)*</td>
<td>60% (59–60%)</td>
<td>64% (63–65%)</td>
<td>65% (64–65%)</td>
<td>57% (55–58%)</td>
<td>63% (62–63%)</td>
</tr>
<tr>
<td>LOS (days) in hospital*</td>
<td>Mean</td>
<td>12.9</td>
<td>14.9</td>
<td>15.5</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>7</td>
<td>10</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Interquartile range</td>
<td>3–16</td>
<td>6–18</td>
<td>7–19</td>
<td>5–20</td>
</tr>
<tr>
<td>Percentage of patients with more than one ventilated hospital admission over the study period, by age at last admission*</td>
<td>4.6</td>
<td>4.5</td>
<td>3.7</td>
<td>2.1</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*P < 0.0001 for comparison between all age groups. CI, confidence interval; IMV, invasive mechanical ventilation; LOS, length of stay.

### Table 2 Overall trend in numbers of ventilated patients 99/00 to 09/10

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>16–39</th>
<th>40–64</th>
<th>65–79</th>
<th>80+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual % increase in absolute numbers of IMV patients (95% CI)</td>
<td>−0.2 (−1.3 to 0.9)</td>
<td>1.6 (0.1 to 3.1)</td>
<td>−0.4 (−2.1 to 1.3)</td>
<td>2.3 (−0.2 to 4.8)</td>
<td>0.6 (−0.9 to 2.0)</td>
</tr>
<tr>
<td>Annual % increase in New Zealand population (95% CI)</td>
<td>0.7 (0.2 to 1.3)</td>
<td>2.5 (0.8 to 4.2)</td>
<td>1.8 (0.0 to 3.6)</td>
<td>3.5 (1.8 to 5.2)</td>
<td>1.7 (−0.4 to 3.8)</td>
</tr>
<tr>
<td>Annual % increase in population rate of IMV (95% CI)</td>
<td>−0.9 (−1.6 to 0.1)</td>
<td>−1.3 (−2.1 to −0.6)</td>
<td>−2.1 (−3.1 to −1.1)</td>
<td>−1.1 (−2.9 to 0.8)</td>
<td>−1.4 (−1.8 to −0.9)</td>
</tr>
</tbody>
</table>

CI, confidence interval; IMV, invasive mechanical ventilation.
The 2-year mortality rate for very elderly patients treated with IMV was 53%. By type of admission, the 2-year mortality rates for this group were 78% for acute medical, 47% for acute surgical and 33% for elective surgical admissions. Both inhospital and 2-year mortality rates for the very elderly are approximately double those aged under 80 years, for all types of admissions (Fig. 2).

The overall 2-year mortality rate for the very elderly declined from 1999 to 2009 by 1.5% per annum, CI −2.6 to −0.4 (Table 3). Within this group, acute surgical admissions decreased (−2.6%, CI −4.4 to −0.8) with no statistically significant change in rates for acute medical or elective surgical patients.

The post-discharge mortality rate for all ventilated patients was higher than the age and sex-matched rates for the general population (Table 4). However, the second-year mortality rate for very elderly patients treated with IMV (5.5%) compares more favourably to the annual mortality rate of the general very elderly population (4.4%) than in younger cohorts, giving a standardised mortality ratio (SMR) of 1.26. This compares with an SMR of 14.6, 6.3 and 2.0 for 16–39 years, 40–64 years and 65–79 years, respectively.

### Discussion

#### Demographics of ventilated patients

In the early days of intensive care units, the very elderly were not admitted, with anecdotal examples of unit admission policies having an age limit of 65–70 years. We postulated that advances in medical interventions, an ageing population with greater life expectancy, changes in societal attitudes to the elderly and possibly even the
ageing of intensive care specialists may lead to changes in the numbers of very elderly treated with IMV.

Absolute numbers of all patients treated with IMV did not change each year over the study period, neither did the subset of very elderly patients. Given population growth over the same period, the overall population IMV rate decreased (1.4% per annum, CI –1.8 to –0.9), and the rate for the very elderly was unchanged (~1.1% per annum, CI –2.9 to 0.8). Should these trends be sustained this suggests that future growth in patients treated with IMV will be driven by absolute increases in the general population, offset by static or falling rates of IMV per capita.

The absolute growth rate for very elderly patients treated with IMV of 2.3% per annum (95% CI –0.2 to 4.8%) is materially lower than the annual growth rate of 5.6% found in a recent large Australasian study of ventilated and non-ventilated ICU very elderly patients. This difference warrants further investigation.

Contrary to our expectations, and to the findings of previous studies, very elderly ventilated patients did not have longer hospital admissions than elderly patients (Table 1), although these data do not include inpatient rehabilitation. In those selected to be treated with IMV, elderly and very elderly patients had clinically similar median and mean hospital length of stay.

IMV in a subsequent admission is uncommon for a patient treated with IMV during a prior hospital admission. Very elderly patients were even less likely to have been ventilated previously in the period of this study than younger cohorts. This is a novel finding and is attributable to the ability to link patient records over time at a national level in New Zealand.

Long-term mortality of ventilated patients

In this study, the overall 2-year mortality rate increased dramatically with age – from 13% in the youngest cohort to 53% in the very elderly (Fig. 1).

Among patients aged over 65 years, studies consistently report higher long-term mortality rates in medical over surgical admissions and unplanned surgery over planned surgery. This ranking of mortality rate is replicated in this study – despite a different definition of ‘surgical admission’. Acute medical admissions had higher mortality rates than acute surgical admissions, which in turn had a higher mortality rate than elective admissions. This difference in mortality is likely to reflect the difference in reversibility of pathology between surgical patients and those requiring admission due to impending organ failure for medical reasons.

Of particular note in this study is the comparison between longer-term mortality in the very elderly ICU patients treated with IMV and the general very elderly population (Table 4). Compared with the age and sex-matched general population rates, the second-year mortality rate is higher than the general population across all age groups of patients treated with IMV – in line with previous studies. However, for the very elderly, the mortality rate among 1-year survivors approaches the mortality rate of age and sex-matched peers in the general population (SMR of 1.26, 95% CI 1.1–1.3). This is in contrast to younger age groups, for whom longer-term mortality rates remain significantly worse than the age and sex-matched general population. This is a novel finding. We postulate that this reflects both the increasing mortality rate with age of the general population and a triaging effect of intensive care illnesses. The high in-hospital mortality for the very elderly may mean that only very well patients survive a severe, acute illness to be discharged and that these patients may have had better pre-existing health than the general population of very elderly.

Trends in long-term mortality of ventilated patients

For the whole cohort, the 2-year mortality rate declined on average over the 10 years of this study by 1.2% per annum (95% CI 0.7–1.7%; Table 3). Among the very elderly, this study finds improvements for acute surgical patients, but no change for medical and elective surgical admissions.

In-hospital mortality rates following ICU admission have generally improved annually. The high in-hospital mortality for the very elderly (39%) might have allowed a much greater percentage improvement in outcomes than other age groups. However, we postulate that the greatest influence on survival of the very elderly is not the intensive care treatment, but the admission selection. It is possible that future improvements in clinical care may be offset by admitting less well very elderly patients with a resulting unchanged overall mortality.

Study limitations

Analysis of critically ill patients is usually reported by ICU admission, rather than IMV status. New Zealand data were only available for the latter. However, this may also represent a more robust clinical benchmark than ICU admission per se given the wide variability in the number of ICU beds per head of population between different

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*Patients in this cohort are deemed a surgical admission if they had a surgical diagnosis, rather than if they had a surgical procedure.
countries, and varying admission criteria for high dependency care to ICU units.

Arbitrary definitions inherent in the data set may limit comparisons with other studies. In particular, the definition of surgical admission is based on diagnosis, not whether an operation was performed. Further, ‘acute’ includes admissions planned up to 6 days before the date of admission.

This study only examines mortality. Functional outcome is an area of relevance and increasing interest in research in survivors of intensive care and is of particular interest in the very elderly where pre-existing frailty is more common. Functional status is an independent prognostic variable, and age over 80 years is an independent predictor of discharge to a care facility. The available data did not enable us to examine functional outcome.

Conclusion

For very elderly patients in New Zealand, both the total number treated with IMV each year and the population rate of IMV are static over the period 1999–2010. The 2-year mortality rate for very elderly patients treated with IMV decreased over the study period, driven by declining mortality in acute surgical patients with no change in acute medical and elective surgical patients.

Although the inpatient mortality rate for the very elderly is high, the post-discharge mortality rate approaches that of the age and sex-matched general population.

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Healthcare professional requirements for the care of adult diabetes patients managed with insulin pumps in Australia


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Key words
insulin, insulin infusion system, health resource, health service need and demand, type 1 diabetes mellitus.

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Abstract

Background: Healthcare professional (HCP) time supporting insulin pump therapy (IPT) has not been documented, yet it is important in planning and allocating resources for effective care.

Aim: This study aims to determine HCP time spent in IPT patient care to inform resource planning for optimal IPT delivery.

Methods: Twenty-four Australian adult IPT-experienced institutions (14 government funded, seven private, three both) collected data between April 2012 and January 2013 prospectively, including: patient demographics, HCP classification, purpose of HCP–patient interaction, interaction mode and HCP time with the patient. A subset of patients was tracked from pre-pump education until stabilisation on IPT.

Results: Data on 2577 HCP-adult patient interactions (62% face-to-face, 29% remote, 9% administrative) were collected over 12.2 ± 6.4 weeks for 895 patients; age 35.4 ± 14.2 years; 67% female; 99% type 1 diabetes, representing 25% of all IPT patients of the institutions. Time (hours) spent on IPT interactions per centre per week were: nurses 5.4 ± 2.8, dietitians 0.4 ± 0.2 and doctors 1.0 ± 0.5. IPT starts accounted for 48% of IPT interaction time. The percentage of available diabetes clinic time spent on outpatient IPT interactions was 20.4%, 4.6% and 2.7% for nurses, dietitians and doctors respectively. Fifteen patients tracked from pre-pump to stabilisation over 11.8 ± 4.5 weeks, required a median (range) of 9.2 (3.0–20.9), 2.4 (0.5–6.0) and 1.8 (0.5–5.4) hours per patient from nurses, dietitians and doctors respectively.

Conclusions: IPT patient care represents a substantial investment in HCP time, particularly for nurses. Funding models for IPT care need urgent review to ensure this now mainstream therapy integrates well into healthcare resources.

Data from this paper have been presented at the International Diabetes Federation World Diabetes Congress, on 4 December 2013, in Melbourne, Victoria, Australia.

Funding/Conflict of interest: N. Cohen receives honoraria from Astra Zeneca, Novartis, Bristol Myer Squibb, Lilly, Sanofi, Novo Nordisk, Abbott and Medtronic, and is an advisory board member for Lilly, Bristol Myer Squibb, Abbott and Sanofi. M. Forbes receives honoraria from Medtronic for educational meetings. T. Greenaway serves on a national advisory board for Sanofi-Aventis and receives research support from Novo Nordisk. N. Harrison received financial support from Medtronic Australia during the conduct of the study. A. Jenkins and D. O’Neal receive research grants, honoraria and travel support from Medtronic, Roche, Novo Nordisk, Lilly and Sanofi. S. Xu received financial support from Merck Sharp & Dohme for conference attendance. The remaining authors declare no duality of interest associated with this manuscript. This work was not supported by external funding.
Introduction

There has been a rapid growth in the number of diabetes patients using insulin pump therapy (IPT) in most developed countries around the world. In Australia, there are approximately 10 500 IPT users (8500 adults), representing 10% of patients with type 1 diabetes (T1D). In the period between 2004 and 2010, new pump users increased by over 30%, while the IPT discontinuation rate is low, at approximately 2%. The United States has the highest level of IPT use worldwide, with an estimated 350 000 to 370 000 IPT users, including those with type 2 diabetes. Of patients with T1D in the United States, 40% are on IPT. In Britain, approximately 6% of those with T1D are on IPT, while other European countries, such as Germany and Norway, have over 15% of T1D patients treated with IPT.

IPT has now become established as a modality in the management of T1D and is supported by a body of evidence. The main motivating factors relate to improved quality of life, reduction in hypoglycaemia and a strong desire to improve glycaemic control. While health economic evaluations of IPT are available and the knowledge base to provide quality care for patients on IPT has recently been detailed, there are no data documenting the healthcare professional (HCP) resources needed to provide appropriate care for IPT users. This information is critical for assessing the health economic impact of the technology and for resource planning to address future demands on the healthcare system as IPT use continues to grow. The aim of this study was to determine prospectively the time spent by diabetes HCP in the care of adult patients managed with IPT to inform appropriate resources for achieving optimal health outcomes with this therapy.

Methods

Site selection

Institutions were selected from both the government-funded and private sectors. Specialist diabetes centres around Australia with recognised expertise in the care of adult patients on IPT and commencing at least one patient on IPT per month were invited to participate in the survey. Centres devoted entirely to paediatric care were not included in the survey. The study was approved by the Human Research Ethics Committee for each participating site as a quality assurance activity.

Data collection

Sites

Each site completed a survey documenting the type of service (government funded or private), whether the centre was accredited by the National Association of Diabetes Centres (NADC) and whether their institution had a clinic dedicated to IPT patients alone. The NADC is a national collective of diabetes centres aimed at promoting integration between specialist centres and improving quality of care for patients with diabetes in Australia. Centres were asked to document an estimate of the total number of diabetes patients managed at their institution, how many were IPT users, the year that the institution initiated their first patient on IPT and the number of new patients commenced on IPT from 1 February 2012 to 1 February 2013. Data collected pertaining to HCP resource availability included the full-time equivalents (FTE) of all HCP involved in the care of diabetes patients at the institution and the FTE of the subset of HCP with IPT expertise. One FTE is defined as working between 35 and 43 h per week, depending on the national standard for different types of HCP. Data were also collected regarding all diabetes clinics at each site, including type of clinic, frequency, duration and HCP availability.

Healthcare professional–patient interactions

All HCP at each site were requested to complete a worksheet each time they interacted with an adult IPT patient. The HCP–patient interaction sheets were designed to minimise intrusion into everyday practice. These were piloted and could usually be completed in 1 min.

Data collected included: patient demographics, HCP classification (doctor, nurse, dietitian, clerical staff, trainer provided by pump manufacturer and other), purpose of the interaction (pre-pump education, pump initiation (specified as overnight, day stay or other), post-initiation stabilisation, routine review, pump renewal, administration and other), modality of the interaction (face-to-face, email, telephone, short message service, fax and Skype/telemedicine) and the time (in minutes) spent with the patient. Doctors were specified as endocrinologist, endocrinology fellow, registrar or resident medical officer. Nurses were specified as registered nurse, registered nurse-credentialed diabetes educator, non-credentialed diabetes nurse educator, clinical nurse specialist – credentialed diabetes educator or nurse practitioner. Dietitians were specified as either dietitian-credentialed diabetes educator or dietitian. In cases where more than one HCP interacted with a patient during a single session, a separate interaction was entered for each HCP, and the time provided on the sheet was entered as the time spent with each individual HCP.

In addition, each site was asked to follow prospectively at least two patients through their entire pump-start process (from pre-pump education to stabilisation up to 3 months post-pump initiation). In cases in which the
nurse or dietitian was sourced from an external service and interaction data were not available, the tracked patient was excluded from analysis.

Pre-pump interactions included assessing patient suitability, patient education and arranging admission for pump initiation. Pump failures were defined as situations requiring change to a new pump, and did not include glucose sensor faults, or line or cannula failures. Administrative/clerical tasks included preparing for an admission, making appointments, registering a patient on the day of admission for a new pump initiation and entering data into a hospital database. Inpatient visits were excluded in the survey, with the exception of admissions for IPT initiation.

After completion of data collection, worksheets were mailed to a data entry coordinator. All patient and HCP details were de-identified. Each patient was allocated a site-specific study number so that multiple interactions with individual patients could be tracked.

Statistical analysis
The HCP-patient interactions were analysed for the number of interactions per patient and total amount of time spent per patient with each HCP group at each IPT stage. The data were stratified for face-to-face and non-face-to-face interactions. The total amount of time spent on IPT interactions was also determined. A separate analysis was performed on patients tracked through the pump-start process. Site sheets were analysed for the total number of HCP, HCP FTE and the number of HCP hours available in diabetes clinics.

Descriptive analyses are reported as mean ± standard deviation, mean (range) or median (range) for skewed data. Analysis was performed using Microsoft Office EXCEL 2007 and STATA/SE 12.1 (Stata Corp, TX, USA).

Results

Site data
All 24 specialist diabetes centres identified as meeting the selection criteria for inclusion as a data collection site were approached and agreed to participate in the survey. Of these, 19 were NADC accredited; 16 had a dedicated IPT service; 14 were government-funded institutions, seven private and three both. They were situated in the Australian states of New South Wales (2), South Australia (3), Tasmania (1), Queensland (2), Western Australia (4) and Victoria (12).

All participating institutions managed young people and adult patients with diabetes (age >15 years). Nine also managed paediatric patients. These institutions collectively managed an estimated 69 144 patients with diabetes (type 1 and 2), of which an estimated 3581 (5.2%) were using IPT (majority T1D). The median number of patients per centre on IPT at the time of data collection was 120 (10–250). The median number of new pump starts per centre over the period February 2012 to February 2013 was 20 (3–98).

Healthcare professional resource availability
The mean FTE for diabetes HCP per centre was 0.9 ± 1.4 (equivalent to 36.0 ± 54.2 h per week) for nurses, 0.4 ± 0.5 (14.0 ± 19.4 h per week) for dietitians and 1.5 ± 1.2 (58.9 ± 47.1 h per week) for doctors. Of these HCP, 66% nurses, 74% dietitians and 61% doctors self-reported IPT expertise. The mean times (h) per centre devoted specifically to ambulatory diabetes care (including non-IPT patient interactions) per week were 19.4 ± 21.9, 7.7 ± 10.5 and 33.3 ± 25.9, for nurses, dietitians and doctors respectively.

Patient baseline characteristics
Interactions with 895 patients were documented. This patient group was estimated to be approximately 25% of the total IPT patients cared for by the participating institutions. Their mean age was 35.4 ± 14.2 years, duration of diabetes was 19.2 ± 11.5 years, and 99% had T1D. Two-thirds were female (6.7% of whom were pregnant at the time of the survey).

Healthcare professional–patient interactions
Total time spent
HCP–patient interaction data were collected at each site over 12.2 ± 6.4 weeks. There was a total of 2577 interactions, with a mean of 2.9 interactions per patient surveyed. Of the total time documented for HCP–patient interactions, 48% of this was for IPT initiation (including pre-pump education, pump initiation and post-initiation stabilisation); 30% was for routine review; and 22% was for pump renewal and changeover from a loan pump to their own pump. Of the 81 patients that had pump initiations, 65 patients were admitted as a day admission, 11 patients were admitted overnight (of which 10 patients stayed one night, and one patient stayed two nights), and five patients were initiated on IPT at a specialist centre without an admission. There were 14 interactions pertaining to the management of pump failures, which involved nine patients from five sites. A mean of 5.4 ± 2.8 h nursing time, 0.4 ± 0.2 h dietitian time and 1.0 ± 0.5 h doctor time per centre per week were spent on IPT patient care.

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With regards to mode of interaction, 62% of all IPT interactions were face-to-face, taking up 85% of total HCP time devoted to IPT; 29% of interactions were remote, taking up 10% of total HCP time; and 9% of interactions were administrative, taking up 5% of total HCP time. Of the remote interactions, 55% were through email, 29% through telephone, 6% through Skype/telemedicine, 3% through short message service, 0.1% through fax and 7% through two or more modalities in a single interaction.

Nursing staff saw the greatest number of IPT patients and spent the greatest amount of time per patient (Table 1). There were 1532 nurse–patient interactions. Of these, 1379 (90%) were with a registered nurse–credentialled diabetes educator, 97 (6.3%) with a non-credentialled diabetes nurse educator, 13 (0.8%) with a nurse practitioner, three (0.2%) with a registered nurse and one (0.1%) with a clinical nurse specialist-credentialled diabetes educator. There were 772 doctor–patient interactions. Of these, 664 (86%) were with an endocrinologist, 104 (13%) with a registrar, three (0.4%) with a resident, one (0.1%) with a Fellow. There were 88 dietitian–patient interactions. Of these, 63 (72%) were with a dietitian and 25 (28%) were with a dietitian-credentialled diabetes educator. Company trainers were utilised in seven of the 24 centres to educate patients in technical aspects of pump operation during initiation, stabilisation, follow up and renewal.

Patients tracked through pump start

Twenty-one pump-start patients from nine centres were tracked through the process of IPT initiation. Six patients were excluded as a member of the team (the dietitian) was sourced externally, and complete data on HCP time utilisation were not available. Data from the remaining 15 T1D patients (three men and 12 women; aged 36.1 ± 15.5 years; duration of diabetes 17.1 ± 9.6 years) from seven sites (four government funded, one private and
two both) are reported from pre-initiation education through to IPT stabilisation.

The median total HCP time taken to commence a patient on IPT was 18.6 h (5.8–46), requiring 14.1 (6–38) interactions over 11.8 ± 4.5 weeks. Two-thirds of the interactions were face-to-face; of these, 36% were at the pre-pump stage, 23% pump initiation and 42% post-initiation stabilisation. Table 2 shows the median time spent per patient with each type of HCP (nurses, doctors, dietitians and company trainers). The greatest HCP time demands were made on nursing staff. Based on these data, for a median of 20 patients per centre commenced on IPT per year, a total of 184 h (60–418) nursing time, 48 h (10–120) dietitian time and 35 h (10–108) doctor time each year is required for IPT initiation and stabilisation alone.

Routine review
Routine review comprised the majority number of patient contacts. The mean interaction times with ambulatory patient attendances at clinics per week were 4.0 ± 3.1 h for nurses, 0.4 ± 0.2 h for dietitians and 0.9 ± 0.5 h for doctors, taking up 20.4%, 4.6% and 2.7% of total available diabetes clinic time for these HCP respectively. These times exclude IPT initiations as they required admission to hospital and did not impact on time devoted to ambulatory care in clinics. The percentage of nursing time devoted to the ambulatory care of IPT patients was disproportionately high in comparison with dietitians and doctors (Fig. 1).

Discussion
The effective provision of adult IPT care requires definition of service delivery requirements, protocols for pump initiation and follow up, human resources necessary for the care of IPT patients and appropriate infrastructure. Services to date have developed in an ad-hoc fashion driven by patient demand and have not necessarily ensured safe and optimal care of patients, nor provided information that could be used for resources planning.

Table 2. Number of healthcare professional–patient interactions and time spent per patient tracked through the pump-start process

<table>
<thead>
<tr>
<th></th>
<th>Nurse</th>
<th>Dietitian</th>
<th>Doctor</th>
<th>Company trainer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interactions/pt</td>
<td>Time/pt (min)</td>
<td>Interactions/pt</td>
<td>Time/pt (min)</td>
</tr>
<tr>
<td>Pre-pump, n = 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face-to-face</td>
<td>1.7</td>
<td>103</td>
<td>1.5</td>
<td>88</td>
</tr>
<tr>
<td>(1–4)</td>
<td>(26–411)</td>
<td></td>
<td>(1–3)</td>
<td>(44–264)</td>
</tr>
<tr>
<td>n = 14</td>
<td>n = 15</td>
<td></td>
<td>n = 11</td>
<td></td>
</tr>
<tr>
<td>Remote/Admin.</td>
<td>1.8</td>
<td>18</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>(1–4)</td>
<td>(9–108)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 5</td>
<td>n = 1</td>
<td></td>
<td>n = 1</td>
<td></td>
</tr>
<tr>
<td>Initiation n = 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face-to-face</td>
<td>1.7</td>
<td>406</td>
<td>1</td>
<td>240</td>
</tr>
<tr>
<td>n = 13</td>
<td>n = 3</td>
<td></td>
<td>n = 8</td>
<td></td>
</tr>
<tr>
<td>Remote/Admin.</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>(1–4)</td>
<td>(9–75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 7</td>
<td>n = 3</td>
<td></td>
<td>n = 3</td>
<td></td>
</tr>
<tr>
<td>Stabilisation (up to 3 months post-initiation), n = 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Face-to-face</td>
<td>2.5</td>
<td>148</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>n = 15</td>
<td>n = 2</td>
<td></td>
<td>n = 8</td>
<td></td>
</tr>
<tr>
<td>Remote/Admin.</td>
<td>3.1</td>
<td>48</td>
<td>Nil</td>
<td>Nil</td>
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<tr>
<td>(1–4)</td>
<td>(9–75)</td>
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<td></td>
</tr>
<tr>
<td>n = 7</td>
<td>n = 3</td>
<td></td>
<td>n = 3</td>
<td></td>
</tr>
<tr>
<td>Entire pump-start process, n = 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face-to-face</td>
<td>5.5</td>
<td>332</td>
<td>1.8</td>
<td>108</td>
</tr>
<tr>
<td>n = 15</td>
<td>n = 15</td>
<td></td>
<td>n = 15</td>
<td></td>
</tr>
<tr>
<td>Remote/Admin.</td>
<td>2.7</td>
<td>40</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>(1–6)</td>
<td>(11–160)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>n = 9</td>
<td>n = 4</td>
<td></td>
<td>n = 4</td>
<td></td>
</tr>
</tbody>
</table>

Fifteen patients were followed through their pump start process over 11.8 ± 4.5 weeks. Number of interactions per patient is expressed as mean (range); time spent per patient is expressed as median (range). Admin., administrative; n = number of patients; pt, patient.
The purpose of the present study was to inform current and future service planning for this growing patient group.

This is the first study worldwide to document prospectively the HCP time commitment required for IPT. Centres across Australia in both the private and government-funded sectors were included. At the time of the survey, there were an estimated 8500 adults on IPT in Australia with 3581 (42%) of these cared for by the participating centres and 895 individuals managed with IPT captured in the present survey (11% of all adult IPT patients in Australia). The data therefore can be regarded as representative of IPT service utilisation in well-equipped diabetes centres treating predominantly adults across Australia.

A major part of IPT care is patient education on the desired behaviours, such as regular glucose monitoring, insulin bolus delivery with meals and carbohydrate counting, important for effective glycaemic control and are typically included in a patient’s diabetes management plan. Therefore, of the groups of HCP involved in IPT care, the greatest time demands were made on nursing staff that play a major role in this regard. Ambulatory interactions with IPT patients, representing 5.2% of all diabetes patients at participating centres in this survey, accounted for a disproportionate 20% of nursing time in diabetes clinics. In order to meet IPT service needs, appropriate reimbursement for nursing staff must be in place to enable the delivery of appropriate patient education, support and follow up. The increased utilisation of company trainers in IPT initiations to educate patients in the basic operation of pumps (‘button pushing’) may also improve the viability of IPT as a mainstream insulin regimen, and so reduce the burden on limited IPT-skilled nursing resources.

Almost one-third of all IPT interactions in this survey were remote, predominantly through email or telephone. While not replacing face-to-face visits these communication modalities may enhance the quality of, and engender efficiencies in patient care. They are attractive from a patient point of view, given reduced demands made their own time in travel and in a clinic waiting room. Indeed, the capacity for remote monitoring is inherent in IPT, which, importantly, has the potential to address diabetes service needs in areas where there is a shortage of such services. Yet presently, a significant proportion of remote care provision is not recognised nor provided for by funding bodies. This is an area requiring urgent attention in order to meet insulin pump service needs adequately and enhance IPT centre viability.

Fourteen pump failures (malfunctions) requiring replacement occurred (in nine patients) out of the 895 patients surveyed over a 3-month data collection period. This equates to a 6% failure rate per year. The pump failure rate is in keeping with reports in the literature, and is therefore not unexpected. However, one should be cautious in interpreting these data as the survey was not designed to determine pump failure rates, and it is possible that some patients may have reported malfunctions directly to the manufacturer who shipped replacement pumps without involvement of the healthcare team.

There were several limitations to the survey, which focused on the HCP, with only very basic patient-related data obtained. The limited focus of the data collection aimed to ensure the maximum adherence of those completing the survey and also to minimise the impact of the survey itself on the time the HCP spent with the patient. The level of adherence with the survey was not determined, and apart from pump initiations, inpatient IPT interactions were not included in the data collection. In addition, a disproportionate number of patients managed with IPT may have been allocated to the more experienced members of the diabetes team. Therefore, it is possible that the true demands made by patients managed with IPT on HCP resources have been underestimated by this survey. Nevertheless, 25% of the estimated total number of IPT patients registered with the centres were included in the survey over the 12 weeks, suggesting that a substantial majority of the HCP–patient IPT interactions were documented. In addition, only IPT-experienced centres were selected for participation in the survey. These centres may be more efficient in the initiation and review of patients on IPT in comparison with centres that care for the occasional IPT patient with less well-established management protocols.

While some young people were managed by centres included in the study, it is unclear if the data can be extrapolated to the paediatric population on IPT. We speculate that HCP requirements may be higher for
children and adolescents, particularly given the need to not only educate parents, but also others carers, such as child-care workers/teachers.

Due to the small number of tracked pump-start patients in our survey, a robust examination of the difference in nursing time spent on IPT interactions between patients with company trainer involvement and those without was not possible. However, this would be a worthwhile avenue for further research.

Lastly, concomitant data were not collected from patients initiated and stabilised on conventional (multiple daily injections) therapy. We therefore cannot directly compare HCP time spent on patients managed with IPT versus those managed with insulin injections though a formal comparison between pump and conventional therapy could form the basis for future research. Nevertheless, disproportionate time demands on HCPs (particularly nurses) were documented, and this is a significant factor that needs to be accounted for in planning for service provision and in the consideration of the cost-effectiveness of IPT.

Conclusions

This study involving a large proportion of adult patients on IPT in Australia demonstrates that the management of these patients requires a substantial yet quantifiable amount of HCP time, which can be used to inform service delivery provision for this therapy. IPT can well integrate into diabetes healthcare resources with appropriate planning and service structures. However, a focus on providing adequate nursing staff is essential to service expansion as this IPT usage continues to grow. Service restructuring, including the introduction of support programmes facilitating IPT implementation by pump manufacturers, may be required to meet future needs, especially in the setting of increasing IPT usage. Concentrating patients managed with IPT in centres of excellence with appropriate allocation and planning of staff resources may also better meet the needs of IPT users, alongside recognition of the capacity of this therapy for remote monitoring.

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POSITION PAPER

Treatment of patients with multiple myeloma who are eligible for stem cell transplantation: position statement of the Myeloma Foundation of Australia Medical and Scientific Advisory Group

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Key words
multiple myeloma, stem cell transplant, therapy.

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Abstract
The survival of patients with multiple myeloma (MM) has improved substantially since the introduction in the late 1980s of high-dose chemotherapy (HDT) supported by autologous stem cell transplantation (ASCT). Further improvements have been observed following the availability of immunomodulatory drugs (IMiD) such as thalidomide and lenalidomide, and the proteasome inhibitor, bortezomib. Here, we summarise the recommendations of the Medical Scientific Advisory Group to the Myeloma Foundation of Australia for patients considered suitable for HDT + ASCT as part of initial therapy. These recommendations incorporate the various phases of treatment: induction, HDT conditioning and maintenance therapy.

Introduction
The treatment paradigm for multiple myeloma (MM) has evolved considerably since the introduction of the so-called ‘novel agents’ namely the immunomodulatory drugs (IMiD) such as thalidomide and lenalidomide and the first-in-class proteasome inhibitor bortezomib. In the era predating these agents (1990s), high-dose chemotherapy (typically high-dose melphalan) supported by autologous stem cell transplantation (HDT + ASCT) was proven superior to conventional-dose chemotherapy as front-line therapy and considered standard of care for transplant-eligible patients.1 At that time, standard-dose chemotherapy was able to achieve a partial response in approximately 50–60% of patients, but patients rarely achieved a complete response (CR) unless the treatment was consolidated with HDT + ASCT. It is now recognised that deeper responses translate to longer duration of response2 − the biological rationale for consolidative HDT + ASCT.

With the advent of IMiD and proteasome inhibitors, deep responses have become more readily achievable (see below). Indeed, with the use of multidrug combinations that incorporate IMiD and/or proteasome inhibitors, the CR rate that can now be achieved with induction and maintenance strategies is comparable with that observed with HDT + ASCT in the 1990s and early 2000s. Consequently, this has conceptually ‘challenged’ the place of front-line HDT + SCT as standard of care in transplant-eligible patients. This manuscript summarises

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the treatment recommendations from the Medical Scientific Advisory Group (MSAG) to the Myeloma Foundation of Australia (MFA) for patients deemed eligible for HDT + ASCT (Fig. 1). These recommendations incorporate the various phases of treatment: induction, stem cell collection, HDT conditioning and maintenance therapy. Recommendations pertaining to patients who are considered to have ‘high-risk’ smouldering myeloma are discussed in our position statement on transplant ineligible patients. The complete guideline on diagnostic work up and treatment is outlined in the Multiple Myeloma Clinical Practice Guideline that is available on http://www.myeloma.org.au.

Figure 1 Treatment algorithm for transplant eligible patients with newly diagnosed symptomatic multiple myeloma. *Suitable candidates for autologous stem cell transplants are generally patients who are aged <75 years with good performance status, no significant comorbidities or frailty. Individual assessment of biological fitness for high-dose chemotherapy (HDT) + autologous stem cell transplantation (ASCT) by the treating physician is advised. Clinical tools such as the haematopoietic stem cell transplant comorbidity index (HCT-CI) may be useful for patients aged above 65 years. **Induction regimens that incorporate bortezomib, thalidomide or lenalidomide improve quality of responses. Patients who are not immediate transplant candidates but in whom ASCT may still be a viable option at relapse should avoid the alkylating agent melphalan so as not to compromise potential stem cell harvest. ***Lower dose melphalan conditioning can be considered in patients aged ≥70 years or younger patients with impaired renal function and comorbidities. alloSCT, allogeneic stem cell transplantation; RIC, reduced intensity conditioning.

Have IMiD and proteasome inhibitor-based combinations superseded HDT and ASTC?

A key question addressed during the development of these recommendations was: are there any situations in which a HDT + ASCT should not be offered to transplant-eligible patients with MM? Firstly, it is important to consider the aims of treatment of MM and whether these can be achieved without HDT + ASCT in the current era. MM remains incurable for the great majority of patients, with a median survival in the modern era of between 4–7 years (depending on prognostic factors), so new therapeutic strategies are aimed at improving overall survival (OS) and quality of life (QOL). It is important to note that the impact on survival by any new treatment strategy can be difficult to demonstrate as long-term follow up is required, and the effect may be confounded by the types of salvage therapy utilised following relapse. Consequently, recognised predictors for survival such as achievement of CR and progression-free survival (PFS) are used as surrogate end-points to facilitate comparisons with evolving treatment strategies. Prior to the era of IMiD and proteasome inhibitors, HDT + ASCT achieved CR in approximately 20–30% of patients with a correlation between the achievement of CR and survival; a recent long-term follow up of 344 patients who received ASCT between the years 1989 and 1998 showed that 35% of patients who achieved CR were still alive after 17 years compared with 11% of non-CR responders.
To improve OS, it is now routine practice to incorporate either IMiD and/or proteasome inhibitors into the pretransplant induction phase with the choice of agent often dependent on regional regulatory issues relating to drug availability. At the time of writing, only thalidomide or bortezomib are available on the pharmaceutical benefits scheme (PBS) in Australia and New Zealand for induction therapy. With double or triple combination induction therapy incorporating IMiD and/or proteasome inhibitors, CR/near(n) CR rates can now be achieved in up to approximately 30–50% of patients, even prior to ASCT. Although clearly a significant achievement, our current definition of CR (as defined by no detectable paraprotein, i.e. immunofixation negativity) is somewhat crude as tumour burden can still be readily detected by flow cytometry or by molecular studies. Indeed, more sensitive techniques in detecting minimal residual disease have demonstrated the prognostic differences between the different ‘depths of CR’: immunophenotypic CR (as defined by no abnormal plasma clone detected on flow cytometry) results in a much more sustained remission/PFS compared with the less sensitive ‘immunofixation negative’ CR (3-year PFS 50% vs 95% for immunophenotypic CR). The deeper the level of CR, the more durable the response appears to be. This in turn correlates strongly with improved survival.

With the aim of maximising depth and durability of response, we believe the key issue is therefore not whether novel agent-based therapy should supersede the need for transplantation, but whether transplantation when incorporated as part of the front-line treatment strategy can augment the rate and quality of CRs to novel agent-based induction. Indeed, recent large trials have consistently shown that pretransplant induction with IMiD and/or bortezomib-based regimens translate into deeper responses post-transplant. With a treatment-related mortality (TRM) of <5%, HDT + ASCT remains one of the most reliable treatment modalities capable of inducing durable and quality responses in MM, and remains integral to our treatment strategy.

**Early versus delayed ASCT**

Conceptually, it is generally accepted that the maximum benefit of HDT, with respect to depth and durability of response, is derived by concentrating the most effective treatment early in the disease course. This is when the existing malignant plasma cell clones are most drug sensitive and patients are more able to tolerate intensive treatment. Indeed, the optimal timing of HDT + ASCT prior to the era of IMiD and proteasome inhibitors was clear – transplantation as part of front-line therapy was considered superior to delaying transplantation until first relapse on the basis of improved event-free survival (EFS) (39 vs 13 months) and average time without symptoms, treatment and treatment toxicity (27.8 vs 22.3 months) compared with when ASCT was ‘delayed’ until first relapse. No difference in OS was demonstrated in this study.

The same question is being readdressed in the era of IMiD and proteasome inhibitors in two randomised phase III trials, the GIMEMA MM-RV-209 trials and EMN MM-RV-441 trials. In both trials, patients age <65 years were given lenalidomide-dexamethasone induction prior to stem cell collection, then randomised to either ASCT or a further six cycles of melphalan, prednisone and lenalidomide (GIMEMA trial) or cyclophosphamide, lenalidomide and dexamethasone (EMN trial). Preliminary combined analysis of these two trials showed superiority of ASCT as part of front-line treatment compared with when ASCT was delayed until relapse, with respect to PFS1 (P < 0.001) and 4-year OS (85 vs 76%, P = 0.027).

In another prospective study that compared lenalidomide and high-dose dexamethasone with lenalidomide and low-dose dexamethasone (Ld) as induction for patients aged <65 years, patients were given the choice either to proceed to HDT + ASCT upfront after four induction cycles or continue with lenalidomide–dexamethasone until disease progression. With the caveats that this trial was not designed to assess the impact of early versus delayed transplant and that this component of treatment was not randomised, post-hoc analysis revealed the probability of survival was substantially higher for those patients undergoing early ASCT compared with patients who continued on with lenalidomide-dexamethasone (3-year survival probability 0.94 vs 0.78 respectively).

In summary, current available data support an early transplant approach as it is associated with longer PFS, time without treatment and emerging OS benefit.

**Tandem versus single ASCT**

Tandem ASCT, in which the second ASCT is planned to occur 3–6 months after the first, was developed in an attempt to increase dose intensity to achieve a deeper and sustained remission. Reported CR rates with single SCT have been approximately 25–35%; that for tandem transplant is approximately 40% with a median EFS and OS of 49 months and 62 months respectively. In a meta-analysis of six randomised control trials of 1803 patients, comparing tandem versus single ASCT for upfront treatment of MM, Kumar et al. reported that while there was a superior overall response rate with tandem ASCT (risk ratio 0.79), there was a significant
Increase in TRM (risk ratio 1.71). Overall, tandem ASCT did not result in improved OS or EFS compared with single ASCT. However, the trials that were included in this meta-analysis were heterogeneous, mainly because of the inclusion of a trial that compared single transplant plus thalidomide maintenance therapy to tandem transplant, which favoured single transplant.19 This trial has been subsequently retracted. When this trial was excluded from the meta-analysis, the heterogeneity disappeared, and there was a statistically significant change in the hazard ratio for EFS but not OS favouring tandem transplant.

In the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON)-65/German Multiple Myeloma Group (GMMG)-HD4 trial that compared VAD (vincristine, doxorubicin, dexamethasone) with PAD (bortezomib, doxorubicin, dexamethasone) followed by ASCT then maintenance with thalidomide (VAD arm) or bortezomib (PAD arm), tandem ASCT emerged on multivariate analysis as a significant factor for improved OS ($P = 0.03$).20 More recently, an integrated analysis was performed of data from phase III European studies in which patients were prospectively assigned to receive either single or double (tandem) ASCT. Double ASCT resulted in superior PFS (med 38 vs 50 months, $P < 0.001$) and OS (5-year estimates: 63% vs 75%, $P = 0.002$).21 Tandem ASCT may therefore be a reasonable strategy, perhaps in selected patients who have had a suboptimal response to first transplant given that subset analyses in previous phase III trials have indicated that tandem transplants seem to primarily benefit patients with less than very good partial response (VGPR) after the first transplantation.22-23 It must be emphasised that consolidation or maintenance therapies with newer agents, and effective salvage therapies in the current era, may well mitigate any OS advantage of tandem ASCT over single ASCT.

**Induction therapy prior to ASCT**

Induction therapy prior to ASCT serves to promptly reduce tumour burden. Deeper pretransplant response is associated with better post-transplant outcome.24 Induction regimens that incorporate IMiD and/or proteasome inhibitors (Table 1) are superior to chemotherapy-only regimens such as the classic infusional VAD, particularly in poor-risk patients such as those with poor cytogenetics or other adverse prognostic features.25-28,40 Two-drug combinations where dexamethasone is combined with thalidomide (TD), lenalidomide (Ld) (low-dose dexamethasone) or bortezomib (BD) are superior to VAD.28,32,40 Of note, Ld or BD achieves CR/VGPR rates of 20–40% prior to ASCT, which is superior to the TD combination that induces CR/VGPR rates of approximately 10–16%.28 Three-drug combinations appear to further improve efficacy with respect to depth of initial response; the addition of a chemotherapy agent, either cyclophosphamide or doxorubicin to thalidomide (CTD, TAD),3,6 bortezomib (CyBorD, PAD)7,8 or lenalidomide (LCD)9 induces CR/VGPR rates between 37% and 65%. Similar impressive efficacy is seen with three-drug regimens that combine IMiD and proteasome inhibitors.24-41 In contrast, no further advantage was seen with a four-drug combination, which instead results in greater toxicity.41 It should be noted that combinations of IMiD and proteasome inhibitors are not currently available through PBS reimbursement in Australia.

There have been no clinical trials that directly compare bortezomib-based regimens to IMiD-based regimens for induction prior to ASCT. One meta-analysis showed that bortezomib-based regimens (BD or BTD) were superior to non-bortezomib-based regimens with respect to PFS and OS,22 but this was not surprising given that the non-bortezomib comparator was VAD or TD, both of which are known to induce only modest responses. Nonetheless, bortezomib certainly induces rapid and quality responses, and given that it can partially mitigate the impact of adverse cytogenetics, bortezomib-based regimens are often used preferentially as first-line induction in transplant eligible patients. A weekly schedule of bortezomib 1.5 mg/m² appears to result in reduced toxicity without compromising efficacy compared with the traditional schedule of bortezomib 1.3 mg/m² days 1, 4, 8, 11 every 21 days.7 Similarly, it appears that weekly subcutaneous bortezomib is better tolerated than intravenous without compromising efficacy in transplant eligible patients, based on preliminary results of a phase II study.41 Please refer to Box 1 for summary of recommendations.

**Stem cell mobilisation**

The most common regimen used to mobilise peripheral blood stem cells for MM patients is high-dose cyclophosphamide with recombinant human granulocyte colony stimulating factor (rhG-CSF), such as filgrastim, 5–10 mcg/kg. The addition of high-dose cyclophosphamide for mobilisation does not necessarily improve depth of response over induction therapy and does not improve CR rates or time to progression (TTP) in patients undergoing ASCT.41 However, using cyclophosphamide for mobilisation has the advantage of increasing the CD34+ cell yield.46 A higher dose of cyclophosphamide (4 g/m²) will give a better CD34+ yield, but may also cause more toxicity requiring hospital admissions compared with cyclophosphamide 2 g/m².47 More recently, plerixafor
Table 1  Induction treatment regimens for upfront treatment of myeloma prior to autologous stem cell transplantation

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Schedule</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD²⁵</td>
<td>Cyclophosphamide 1g/m² IV D1</td>
<td>Post-transplant ORR 81% (similar to VAD with ORR of 80%)</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 40 mg D1-4, 9-12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycles repeated every 21 days for 2-3 cycles prior to ASCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 100 mg/m² po D1, 2, 3, 4</td>
<td>ORR 66% (CR 9%) post-CID</td>
</tr>
<tr>
<td></td>
<td>Idarubicin 10 mg/m² po D1, 2</td>
<td>ORR 80% (34% CR) post-AuSCT</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 40 mg po daily, D 1–4, 8–11, 15–18 for cycle 1; days 1–4 for cycles 2–4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycles repeated 21 days for 3–4 cycles prior to ASCT</td>
<td></td>
</tr>
<tr>
<td>PCAB²⁶</td>
<td>Cyclophosphamide 30 mg/m² IV D1</td>
<td>ORR 81% (similar to VAD with ORR of 80%)</td>
</tr>
<tr>
<td></td>
<td>Carmustine 30 mg/m² IV D1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 600 mg/m² IV D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prednisolone 60 mg/m² po D1-5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pegfilgrastim 6 mg sc D2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycles repeated every 21 days for 2–3 cycles prior to ASCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORR 48% (41% PR, 7% CR) post-ASCT</td>
<td></td>
</tr>
<tr>
<td>TD²⁷–⁳⁰</td>
<td>Thalidomide 200 mg po daily</td>
<td>Pretransplant ORR varies from 64% to 76%</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 40 mg po daily D1-4</td>
<td>ORR 76% with thalidomide-dexamethasone versus 52% VAD, p &lt; 0.001²⁸</td>
</tr>
<tr>
<td></td>
<td>Cycles repeat every 4 weeks for 3–4 cycles prior to ASCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORR 66% (CR 9%) post-CID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORR 80% (34% CR) post-AuSCT</td>
<td></td>
</tr>
<tr>
<td>TAD²⁹</td>
<td>Thalidomide 200 mg po daily</td>
<td>ORR 72% versus 54% with VAD, p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 20 mg po daily of and day after bortezomib</td>
<td>CR + VGPR higher post-ASCT in TAD arm (49% vs 32%, p &lt; 0.001)</td>
</tr>
<tr>
<td>PAO³⁰,³¹</td>
<td>Bortezomib 1.3 mg/m² IV D1, 4, 8, 11</td>
<td>CRinCR 22% post-induction</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 20 mg on day of and day after bortezomib</td>
<td>CRinCR 38% post-ASCT</td>
</tr>
<tr>
<td></td>
<td>Cycles repeat every 21 days for 3–4 cycles prior to ASCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORR 95%; 65% ≥ VGPR, 24% CR</td>
<td></td>
</tr>
<tr>
<td>CyBorD/BCD³²,³³</td>
<td>Bortezomib 1.3 mg/m² IV D1, 4, 8, 11</td>
<td>Assessment following ± ASCT: ORR 95%, 81% ≥ VGPR, 43% CR</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 300 mg/m² po D1, 8, 15, 22 (or cyclophosphamide 900 mg/m² IV D1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 20 mg po on day of and day after bortezomib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycles repeated every 21 days x for 3–4 cycles prior to ASCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bortezomib 1.5 mg/m² wc D1, 8, 15, 22</td>
<td>ORR 93%; 2VGPR 60% post-induction</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 300 mg/m² po D1, 8, 15, 22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 20 mg po on day of and day after bortezomib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycles repeated every 28 days x for 3–4 cycles prior to ASCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 40 mg po weekly</td>
<td>CR/VGPR 42% post-induction</td>
</tr>
<tr>
<td></td>
<td>Cycles repeated every 21 days x for 3–4 cycles prior to ASCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORR 88%, 2VGPR 61% post-induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lenalidomide 25 mg po daily D1–21 every 28 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 40 mg po daily D1–21 every 28 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycles repeated every 21 days x for 3–4 cycles prior to ASCT</td>
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<td>Or</td>
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<tr>
<td></td>
<td>Lenalidomide 25 mg po daily D1–21 every 28 days</td>
<td></td>
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<td></td>
<td>Dexamethasone 40 mg po weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycles repeated every 21 days x for 3–4 cycles prior to ASCT</td>
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</tr>
<tr>
<td></td>
<td>Until disease progression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LCD³⁴</td>
<td>Lenalidomide 25 mg po daily D1–21 every 28 days</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 300 mg/m² po daily D1, 8, 15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 40 mg po daily D1–21 every 28 days</td>
<td></td>
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<tr>
<td></td>
<td>Cycles repeated every 21 days x for 3–4 cycles prior to ASCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BTD³⁴</td>
<td>Bortezomib 1.3 mg/m² IV D1, 4, 8, 11</td>
</tr>
<tr>
<td></td>
<td>Thalidomide 200 mg po D1–4</td>
<td>CR was 57% post-ASCT</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 40 mg po on day of and day after bortezomib</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycles repeated every 21 days x for 3–4 cycles prior to ASCT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORR 96%; CRinCR 44% post-induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORR 100%; CRinCR = 78% post-ASCT</td>
<td></td>
</tr>
</tbody>
</table>

This table summarises the commonly used induction regimens and is not intended to be exhaustive. Please refer to recommendations regarding induction therapy. ASCT, autologous stem cell transplantation; CR, complete response; IV, intravenous; nCR, near CR; ORR, overall response rate; VAD, vincristine, doxorubicin, dexamethasone; VGPR, very good partial response.
Box 1 Recommendations regarding induction therapy

- Transplant-eligible patients should be treated with three to six cycles of induction prior to ASCT (grade A recommendation, level 1B evidence).
- VAD is no longer a recommended induction regimen (grade A recommendation, level 1B evidence).
- The incorporation of proteasome inhibitors, thalidomide or lenalidomide as part of front line induction therapy (Table 1) improves quality of responses and is considered standard of care. Currently, only bortezomib and thalidomide but not lenalidomide are available on the Australian PBS for induction therapy for patients with newly diagnosed MM.
- Three-drug combinations appear more efficacious than two-drug combinations (grade B recommendation, level 2A evidence). Four-drug combinations are more toxic without added efficacy and are not recommended (grade A recommendation, level 1B evidence).
- The choice of induction therapy (Table 1) is dependent on local availability/access to novel therapeutic agents and should take into consideration the patient’s prognostic indices and comorbidities, for example:
  - For patients categorised as having high-risk MM (Table 2) or with renal impairment, the use of bortezomib early in the disease course should be considered (grade A recommendation, level 1B evidence).
  - For patients with pre-existing neuropathy, thalidomide or bortezomib should be used with caution with appropriate dose attenuation upon worsening of neuropathic symptoms. A weekly schedule of bortezomib 1.5 mg/m² and subcutaneous route of administration appear to significantly reduce neurotoxicity compared with the traditional bortezomib schedule of 1.3 mg/m² IV on days 1, 4, 8, 11 every 21 days.
  - For patients with severe renal impairment, lenalidomide-based regimens are not the induction of choice because of renal clearance of lenalidomide.
  - For patients with previous history or at high-risk of thromboembolic complications, thalidomide and lenalidomide, although not absolutely contraindicated, should be avoided if other effective induction options are available. For recommendations with respect to thromboembolic prophylaxis for patients treated with thalidomide or lenalidomide, please refer to the MSAG Multiple Myeloma Clinical Practice Guideline (http://www.myeloma.org.au).
- Plerixafor in combination with rhG-CSF significantly improves stem cell mobilisation and is reserved for patients who fail to mobilise adequately on cyclophosphamide plus rhG-CSF, or rhG-CSF alone (grade B recommendation, level 2B evidence).
- rhG-CSF alone may be adequate for the initial attempt of stem cell mobilisation after thalidomide or bortezomib-based induction therapy. However, combination rhG-CSF and high-dose cyclophosphamide may be required after lenalidomide-based induction therapy, and it is recommended that stem cell mobilisation is attempted before patients have received more than four treatment cycles (grade B recommendation, level 2B evidence).
- Plerixafor in combination with rhG-CSF significantly improves stem cell mobilisation and is reserved for patients who fail to mobilise adequately on cyclophosphamide plus rhG-CSF, or rhG-CSF alone (grade B recommendation, level 2B evidence).

Box 2 Recommendations regarding stem cell mobilisation

- Stem cell mobilisation regimen should follow institution protocol.
- Stem cells can be mobilised with rhG-CSF alone or rhG-CSF (10 mcg/kg) in combination with high-dose cyclophosphamide (2–4 g/m²).
- The use of high-dose cyclophosphamide has the advantage of increasing CD34+ yield but is also associated with more toxicity.
- rhG-CSF alone may be adequate for the initial attempt of stem cell mobilisation after thalidomide or bortezomib-based induction therapy. However, combination rhG-CSF and high-dose cyclophosphamide may be required after lenalidomide-based induction therapy, and it is recommended that stem cell mobilisation is attempted before patients have received more than four treatment cycles (grade B recommendation, level 2B evidence).
- Targeted radiographic imaging if indicated.

Box 3 Recommendations regarding follow up post-ASCT

Post-ASCT, patients should be followed up monthly until stable, then 3 monthly or less frequent if there appears to be disease stability (grade C recommendation, level 4 evidence).

- Follow up assessment should include:
  - Clinical assessment.
  - Serum ± urinary protein electrophoresis (immunofixation not required).
  - Serum free light chains.
  - FBE, U&E, Ca²⁺.
  - Targeted radiographic imaging if indicated.

Post-ASCT, patients should be followed up monthly until stable, then 3 monthly or less frequent if there appears to be disease stability (grade C recommendation, level 4 evidence).

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  - Clinical assessment.
  - Serum ± urinary protein electrophoresis (immunofixation not required).
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  - FBE, U&E, Ca²⁺.
  - Targeted radiographic imaging if indicated.

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- Follow up assessment should include:
  - Clinical assessment.
  - Serum ± urinary protein electrophoresis (immunofixation not required).
  - Serum free light chains.
  - FBE, U&E, Ca²⁺.
  - Targeted radiographic imaging if indicated.

Bortezomib and thalidomide on their own do not appear to impair stem cell mobilisation⁶⁰ in patients who have received fewer than four induction treatment cycles. Recent reports have indicated that thalidomide and oral cyclophosphamide, two agents that have not been shown to impact stem cell mobilisation individually, may induce a higher rate of stem cell mobilisation failure when used in combination.⁵⁰ Lenalidomide has been reported to reduce the number of CD34+ cells collected.³¹ Mobilisation using rhG-CSF alone after lenalidomide-based induction therapy may be inferior to rhG-CSF plus lenalidomide, a combination that may induce a higher rate of stem cell mobilisation failure when used in combination.⁵⁰
to combination therapy using rhG-CSF and high-dose cyclophosphamide, and the latter should be considered for stem cell mobilisation. It is strongly advised to mobilise patients prior to receiving four cycles of lenalidomide-based induction therapy. Please refer to Box 2 for summary of recommendations.

Monitoring after ASCT

The average TTP for patients after HDT and ASCT is in the order of 2–4 years for younger patients and shorter for older patients. The final magnitude of response post-ASCT should be assessed after 2–3 months. Patients should be followed up with clinical and laboratory assessments, looking for evidence of relapse/progression. Testing should include serum or urinary paraprotein levels (SFLC levels are used in patients with unmeasurable paraprotein in blood or urine), full blood count, serum calcium levels and renal function. In assessing response, it is important not to misinterpret the emergence of oligoclonal bands as relapsed disease or clonal evolution. Oligoclonal response after primary therapy is a well-recognised event, and can appear as multiple oligoclonal bands in serum and/or urine immunofixation; it is thought to be related to immune reconstitution and is associated with a favourable outcome. Initial follow up for patients is usually monthly until stable, then 3 monthly or less frequent subsequently if there appears to be disease stability. Please refer to Durie et al. for uniform response criteria to assess response and relapse after treatment. Please refer to Box 3 for summary of recommendations.

Consolidation and maintenance therapy post-ASCT

Consolidation following ASCT refers to a short treatment course that improves depth of response. At the current time, there are insufficient data to determine if consolidation therapy improves long-term outcome in MM. The VCAT (Bortezomib Consolidation after Transplant) study is currently ongoing and may answer this question in due course. In contrast, maintenance therapy with thalidomide is well tolerated, improves PFS and possibly OS. Treatment is generally tolerated for a median of approximately 12 months. Toxicity, in particular peripheral neuropathy, is the main reason for early thalidomide discontinuation. Lenalidomide maintenance post-ASCT has been assessed in two phase III studies. A reduced risk of disease progression by 50–52% (P < 0.001) was seen, and one study showed a significant reduction in

Box 4 Recommendations regarding maintenance therapy post-ASCT

- Maintenance therapy with thalidomide 100 mg daily with or without corticosteroids is recommended in patients following first-line treatment with HDT and ASCT (grade A recommendation, level 1A evidence).
- Thalidomide ± prednisolone maintenance post-ASCT should continue for approximately 12 months. The benefit of maintenance beyond 12 months remains to be proven (grade A recommendation, level 1A evidence).
- Lenalidomide maintenance post-ASCT is well tolerated, improves PFS and possibly OS (grade A recommendation, level 1B evidence). At present, lenalidomide is not registered for this indication, and hence we cannot currently routinely recommended lenalidomide maintenance.
- The dose schedule and role of maintenance bortezomib is still unclear, and bortezomib is not registered for this use. Bortezomib maintenance is not recommended (grade C recommendation, level 4 evidence).

Box 5 Recommendations regarding alloSCT

- Currently, alloSCT is still considered investigational and should ideally be performed in the setting of a clinical trial (grade C recommendation, level 4 evidence).
- Young patients with high-risk MM (Table 2) who are considered potentially suitable for alloSCT should be referred early to the transplant physician at the outset of treatment (grade C recommendation, level 4 evidence).

Box 6 Recommendations for patients with high-risk MM

The optimal management for patients with high-risk MM remains uncertain. There is no proven risk stratification approach:
- Consider using bortezomib-based regimen as part of induction treatment (grade A recommendation, level 1B evidence).
- Consider early referral for allogeneic stem cell transplant consideration for selected patients with HLA-matched sibling. However, the role of allogeneic stem cell transplant, even in the high-risk setting is still unclear and requires discussions with both the transplant and treating haematologist early in the disease course (grade C recommendation, level 4 evidence).
- Consider tandem autologous stem cell transplant (grade B recommendation, level 2B evidence).

HLA, human leucocyte antigen; MM, multiple myeloma.

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risk of death. Grade ≥3 neutropenia was the most frequent adverse event. A higher incidence of secondary malignancies was noted in the lenalidomide arm in both studies (7.8–8.5% vs approximately 3% placebo). With respect to lenalidomide-associated secondary primary malignancies, a recent meta-analysis has shown that the risk pertains to secondary haematological malignancies and is closely related to the use of oral melphalan. The current general consensus is that the benefits of lenalidomide treatment with lenalidomide until disease progression appear to outweigh the risks, although longer-term follow up is required. It is unknown whether maintenance with lenalidomide is equivalent to maintenance with thalidomide in terms of efficacy or toxicity. It is assumed that bortezomib, like thalidomide or lenalidomide, likely improves depth of response when used as consolidation or maintenance. However, the design of available studies, which incorporated different induction and consolidation arms, makes it difficult to elucidate the impact of bortezomib maintenance on survival. As such, no firm conclusions regarding bortezomib maintenance can be made. Please refer to Box 4 for summary of recommendations.

Allogeneic stem cell transplant

‘Graft versus myeloma (GVM)’ effect has been shown to exist in the setting of allogeneic stem cell transplantation (alloSCT). However, while this may give rise to some long-term durable remissions, myeloablative alloSCT is associated with a high TRM of up to 50%. The subsequent introduction of reduced intensity conditioning (RIC) alloSCT has led to a lower TRM, approximately 10–15% at 1 year, while maintaining the GVM effect. Three prospective trials have been published that assessed the role of alloSCT as part of planned initial therapy in patients with MM. In the Intergroupe Francophone du Myelome (IFM)99-03 study, patients with high-risk (del13q + β2-microglobulin > 3 mg/mL) and available sibling donors underwent MEL200 (melphalan 200 mg/m²) ASCT followed by RIC alloSCT with antithymocyte globulin, busulphan and fludarabine conditioning. Patients without a donor had a second ASCT. At the time of initial reporting, median EFS and OS were similar in the two cohorts, EFS 35 versus 32 months, P = ns (not significant), and OS 47 versus 35 months, P = ns, in ASCT + RIC alloSCT versus tandem ASCT respectively. However, after longer follow up, OS was found to be significantly inferior in patients assigned to RIC alloSCT. An Italian randomised study also compared tandem ASCT versus ASCT followed by RIC alloSCT (non-myeloablative total body irradiation conditioning). Poor prognostic features were not required for trial entry. A superior long-term outcome was seen in patients who had available sibling donors (OS: 80 vs 54 months, P = 0.01; EFS: 35 vs 29 months, P = 0.02). In the Spanish PETHEMA (Spanish myeloma group) trial, comparisons were made between a second ASCT and RIC (melphalan and fludarabine) alloSCT in a group of patients who achieved VGPR to their first ASCT. A higher rate of CR and a plateau in PFS in favour of RIC alloSCT was seen (40% vs 11%, P = 0.001) in this group. However, because of a higher TRM and graft versus host disease, no statistical difference in EFS and OS was observed. Finally, interim results from the Blood and Marrow Transplant Clinical Trials Network 0102 Trial showed equivalent 3-year PFS and OS for tandem auto-auto versus auto-allo stem cell transplant both high-risk and standard-risk MM patients; 2 Gy total body irradiation was used as the non-myeloablative conditioning regimen in the alloSCT arm. There was a trend to lower late PFS and TTP/relapse in the auto-alloSCT arm in the high-risk group (P = 0.09); however, no added benefit from auto-alloSCT was seen in the standard-risk group over tandem ASCT because of increased TRM. Please refer to Box 5 for summary of recommendations.

High-risk multiple myeloma

Several factors are known to confer a poorer prognosis in patients with MM (Table 2). These include older age, higher International Stage System (ISS) stage, high lactate dehydrogenase (LDH), high plasma cell labelling index and the cytogenetic abnormalities: 13q deletion (identified by standard cytogenetic), t(4;14), t(4;16) and 17p deletion (as identified by fluorescent in situ hybridisation (FISH)). Amplification of chromosome 1q21 (by FISH) has also been shown to be associated with both shorter time to disease progression and poorer prognosis. By definition, patients with high-risk MM are considered those with an OS of 2 years or less despite treatment with IMiD and proteasome inhibitors. The most robust factors that are consistently associated with such poor survival are higher ISS stage and the cytogenetic abnormalities 17p deletion and t(4;14). Recently, this has led to a proposed revised(R)-ISS risk stratification system that incorporates ISS stage, LDH and high-risk iFISH (del17p and t(4;14)). The R-ISS risk stratification system (Table 2) was recently shown to identify clearly three different MM prognostic groups in patients who were treated in the era of IMiD and proteasome inhibitors. If this is confirmed by prospective evaluation, it will likely supersede the current ISS staging system.

Several reports have confirmed that bortezomib is effective even in the presence of poor risk cytogenetics (13q deletion, t(4;14), amp1q21 and perhaps even 17p deletion). Preliminary data suggest that the same
Table 2  Factors associated with poorer prognosis in multiple myeloma

<table>
<thead>
<tr>
<th>High-risk factors</th>
<th>The following tests for high-risk disease are routinely available in Australia and are recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS (International Stage System) III (Serum β2 microglobulin &gt; 5.5 mg/L)</td>
<td>Albumin</td>
</tr>
<tr>
<td>Conventional cytogenetics</td>
<td>Conventional cytogenetics‡</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>t(14;16)</td>
</tr>
<tr>
<td>Del17p</td>
<td>Del17p</td>
</tr>
<tr>
<td>1q21 amplification</td>
<td>1q21 amplification.</td>
</tr>
<tr>
<td>Plasma cell labelling index ≥3%</td>
<td>Plasma cell labelling index (by flow cytometry)§</td>
</tr>
<tr>
<td>High lactate dehydrogenase (LDH)</td>
<td>LDH</td>
</tr>
</tbody>
</table>

Revised (R)-ISS risk stratification model‡

<table>
<thead>
<tr>
<th>R-ISS I</th>
<th>The following tests for high-risk disease are routinely available in Australia and are recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS I (serum β2 microglobulin &gt; 3.5 mg/L and serum albumin &gt; 35 g/L) AND</td>
<td>Normal LDH AND</td>
</tr>
<tr>
<td>No high-risk iFISH profile (defined as del17p and/or t(4;14) and/or t(14;16))</td>
<td>No high-risk iFISH profile (defined as del17p and/or t(4;14) and/or t(14;16))</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R-ISS II</th>
<th>Patients failing to meet criteria for R-ISS I or III</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS III (serum β2 microglobulin &gt; 5.5 mg/L) AND</td>
<td>High-risk iFISH OR</td>
</tr>
<tr>
<td>High-risk iFISH OR</td>
<td>High LDH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R-ISS III</th>
<th>The following tests for high-risk disease are routinely available in Australia and are recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS I (serum β2 microglobulin &gt; 3.5 mg/L and serum albumin &gt; 35 g/L) AND</td>
<td>Normal LDH AND</td>
</tr>
<tr>
<td>No high-risk iFISH profile (defined as del17p and/or t(4;14) and/or t(14;16))</td>
<td>No high-risk iFISH profile (defined as del17p and/or t(4;14) and/or t(14;16))</td>
</tr>
</tbody>
</table>

Conclusions

In transplant-eligible patients, ASCT remains a cornerstone of front-line therapy to maximise depth and durability of CR in our ultimate quest for improved survival while maintaining QOL. Based on current available data, we recommend that the most appropriate strategy for frontline treatment in transplant-eligible patients with MM should include an induction regimen containing either bortezomib or an IMiD, followed by HDT + ASCT, that thalidomide maintenance (Fig. 1). The routine use of bortezomib or lenalidomide post-transplant as consolidation or maintenance is yet to be proven superior to thalidomide maintenance. We believe that a national consensus for treatment algorithm of MM will improve patterns of care in Australia; the clinical practice guideline for MM will be updated by the MSAG to the MFA on an annual basis.

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BRIEF COMMUNICATIONS

Statin utilisation patterns in older Australians living in residential care: 1-year prevalence study

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Key words statin, older people, limited life expectancy, deprescribing, residential care.

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Abstract Despite controversy over the risks and benefits of statin therapy, statins continue to be commonly used medicines by older people. In a cohort study of participants aged ≥70 years (n = 540) living in residential care, Sydney, we found that the proportion of statin users decreased gradually from the baseline of 33.1% to 31.3% at 6 months (P = 0.13) and to 28.7% over 1 year (P = 0.002). Prevalence of statin use decreased with increasing age, with individuals aged ≥90 years being more likely to discontinue or deprescribe statins. The patterns of statin use did not change according to increasing baseline dose or baseline indication.

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are commonly used preventative medicines by older people. In Australia, statins are used by 43% of community-dwelling people aged ≥75 years.1 Other recent international studies of older people reported statin prevalence of 12.9–33.1%.2,3 Although the benefits of statins in reducing the risk of cardiovascular events are well established in younger populations, the evidence on the benefits of statins in older people is less clear.4 The current evidence supports statin use for secondary prevention of cardiovascular events and death in people aged 65–80 years and in older people with a high risk of cardiovascular disease.5,6 Moreover, statin therapy has been associated with adverse events in older people.4,7 Older people with multi-morbidity and polypharmacy are at greater risk for statin–drug interactions and consequent adverse drug reactions.8

There are inconsistent data in relation to utilisation patterns of statins in older people. A recent USA study conducted in community-dwelling older people showed that statin use substantially increased over a decade (1997/1998–2007/2008) from 12.9% to 39.1%.9 However, other studies reported decrease in statin trends among older people, in particular among those aged ≥80 years.10,11 Moreover, it is unclear whether statin utilisation patterns are increasing or decreasing in older people with increased functional impairment, multi-morbidity and limited life expectancy such as those living in residential aged care facilities (RACF). Among RACF individuals, continuing preventative drugs including statins is unlikely to be of clinical benefit as time needed to obtain the expected treatment effects is likely to be longer than the estimated life expectancy.4 The aim of this study is to describe the prevalence and patterns of statin use over 1 year among older people living in residential care and to correlate patterns of statin use according to baseline age, dose and indication.

We performed a cohort study of RACF participants (n = 602) who took part in a multicenter cluster-randomised controlled trial in Australia.12 Individuals were eligible if they were ambulant, aged ≥70 years, likely to survive for 12 months based on the Implicit Illness Severity Scale (IISS) and as judged by facility staff at the time of recruitment to the study.12,13 The current analysis was restricted to 540 participants with complete medication data over 1 year. The study was approved by the Northern Sydney Central Coast Area Health Service Human Research Ethics Committee (0512-240M).

Medication history was taken from the individual or from signed nursing administration records for all funding: D. Gnjidic is supported by National Health and Medical Research Council Early Career Fellowship.

Conflict of interest: None.

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Table 1 Baseline characteristics of the study population according to statin use (n = 540)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total population</th>
<th>Statin users (n = 179; 33.1%)</th>
<th>Non-users (n = 361; 66.9%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) (years)</td>
<td>85.5 ± 6.4</td>
<td>83.9 ± 5.8</td>
<td>86.4 ± 6.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age groups, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–79 years</td>
<td>100 (18.5)</td>
<td>41 (22.9)</td>
<td>59 (16.3)</td>
<td></td>
</tr>
<tr>
<td>80–89 years</td>
<td>288 (53.3)</td>
<td>111 (62.0)</td>
<td>177 (49.0)</td>
<td></td>
</tr>
<tr>
<td>≥90 years</td>
<td>152 (28.2)</td>
<td>27 (15.1)</td>
<td>125 (34.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>391 (72.4)</td>
<td>122 (68.2)</td>
<td>269 (74.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Modified co-morbidity index, mean (SD)</td>
<td>2.5 ± 1.7</td>
<td>3.2 ± 1.7</td>
<td>2.1 ± 1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of drugs, mean (SD)</td>
<td>6.0 ± 3.0</td>
<td>7.5 ± 2.9</td>
<td>5.2 ± 2.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Polypharmacy, n (%)</td>
<td>350 (64.8)</td>
<td>150 (83.8)</td>
<td>200 (55.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hyperpolypharmacy, n (%)</td>
<td>76 (14.1)</td>
<td>43 (24.0)</td>
<td>33 (9.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Indication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>90 (16.7)</td>
<td>10 (5.6)</td>
<td>80 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>450 (83.3)</td>
<td>169 (94.4)</td>
<td>281 (77.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SD, standard deviation.

At baseline, 33.1% of participants reported using statins (Table 1). Statin users were younger (P < 0.0001), had more co-morbidity (P < 0.0001) and were more likely to be exposed to both polypharmacy (P < 0.0001) and hyperpolypharmacy (P < 0.0001). Among statin users at baseline, 16.3% (n = 29) were exposed to statin–drug interactions. The most common drug interactions included co-prescription of warfarin (7.3%) and diltiazem (3.9%) with statins.

The patterns of statin utilisation decreased gradually from the baseline of 33.1% to 31.3% at 6 months (P = 0.13) and to 28.7% at 12 months (P = 0.002) (Table 2). Among statin users at baseline (n = 179), 140 (78.2%) participants were still using statins at 12 months, whereas 39 (21.8%) discontinued statins. Moreover, prevalence of statin use decreased with increasing baseline age over 1 year. Between baseline and 12 months, the proportion of statin users among age group of 70–79 years decreased from 41.0% to 37.0%; age group 80–89 years from 38.5% to 34.0%, whereas the proportion of users among participants aged ≥90 years decreased from 17.8% to 13.2% (P < 0.0001). At baseline, 15.2% of participants reported use of high-dose statins, 12.6% medium-dose statins and 5.0% reported low-dose statin use. The

Table 2 Patterns of statin utilisation over 1 year

<table>
<thead>
<tr>
<th>Statin use at baseline*</th>
<th>Statin use at 6 months, n (%)†</th>
<th>Statin use at 12 months, n (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>156 (28.9)</td>
<td>140 (25.9)</td>
</tr>
<tr>
<td>No</td>
<td>23 (4.3)</td>
<td>39 (7.2)</td>
</tr>
<tr>
<td>Yes (n = 179; 33.1%)</td>
<td>156 (28.9)</td>
<td>140 (25.9)</td>
</tr>
<tr>
<td>No (n = 361; 66.9%)</td>
<td>23 (4.3)</td>
<td>39 (7.2)</td>
</tr>
<tr>
<td>Total</td>
<td>179 (33.1)</td>
<td>159 (28.7)</td>
</tr>
</tbody>
</table>

†Percentage of total study population.
patterns of statin use did not change according to baseline dose or indication over 1 year. Of those who stopped statins (n = 39) at 12 months, 12.8% (n = 5) were taking statins for primary prevention at baseline. Of participants that started statins (n = 15) at 12 months, 33.3% (n = 5) had a diagnosis of stroke at baseline.

To our knowledge, this is the first study to describe prevalence and patterns of statin utilisation in older Australians living in residential care. The proportion of statin users gradually decreased over 1-year period in older people living in residential care. Statin use decreased according to the increasing baseline age, with individuals aged ≥90 years being more likely to discontinue statins.

Statin exposure in our study population was similar to other recent studies, but different to studies of older people recruited in the late 1990s. The patterns for reduced statin use in older individuals, in particular those aged ≥80 years, recruited during 1998–2002 and 1999–2008, have been reported in studies. A study conducted in Sydney nursing homes reported decline in cardiovascular drug use including diuretics during the period 1993–2003. However, patterns in statin use were not reported in that study. Other studies have reported increase in statin use over time. In the USA study of patients with symptomatic coronary artery disease admitted to nursing homes after hospitalisation, statin use increased from 1.2% to 31.8% over 11 years (1994–2004). Minimising statin use in older people with multi-morbidity, limited functioning and low life expectancy such as residential care residents may be appropriate as older individuals are at increased risk from statin adverse effects, and the clinical benefits of preventative drugs including statins is unclear in this population. Achieving quality use of medicines in residential care is challenging, and it may require including physicians such as geriatricians and palliative care physicians in the residential care teams to provide comprehensive care in this setting.

In our study, 15.2% of statin users at baseline reported use of high-dose statins. Exposure to higher doses of statins does not increase the effectiveness, but does increase the risk of adverse effects including myopathy and diabetes. Moreover, among statin users, 16.9% were exposed to potential statin–drug interactions. Exposure to statin–drug interactions has been associated with an increased risk of hospitalisation, hospitalisation with rhabdomyolysis and all-cause mortality in older people. Given the common use of statins in older people living in residential care, and co-prescription of potentially interacting drugs, the potentially preventable statin–drug interactions remain clinically important.

There are important limitations to our study. Data on detailed clinical information and medical diagnosis, which may explain statin-prescribing practices, were unavailable. The presence of unstable versus stable atherosclerotic cardiovascular disease may have impacted on the decision to continue or to deprescribe a statin. We have attempted to describe statin utilisation patterns according to the indication using medications as surrogate measures of cardiovascular diseases. We did not have information on how long the participants had been taking statins prior to study enrolment. Moreover, we had no data related to the statin therapy adherence. Non-adherence is more common in older people with poor cognition such as those living in RACF. However, people with cognitive impairment are likely to have supervision for medication administration in RACF. Our findings may not be generalisable to older people living in RACF as the cohort was drawn from a randomised controlled trial study with specific inclusion criteria. This study was based in low-level RACF, excluding those in high-care units or nursing homes. Moreover, excluding individuals with a high IISS score means that those most likely to die within 1 year were less likely to take part in the study.

This study found that older people living in residential care setting commonly take statins. When prescribing statins for older people living in residential care setting, physicians should consider the treatment benefits against the multi-morbidity, limited life expectancy and potential harms. More research is needed to understand better statin utilisation patterns in older people living across different settings and to establish the clinical impacts of continuing and stopping statin therapy in older frail people with multi-morbidity and low life expectancy.

Acknowledgement

The FREEDOM trial was registered on the Australian Clinical Trials Registry (ACTR number: ACTRN12607000089437).
Leprosy: diagnosis and management in a developed setting

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Key words
leprosy, leprosy reaction, Hansen disease, erythrom nodosum leprosum, reversal reaction

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Abstract

Leprosy remains an important global health concern, but little has been published about its diagnosis and management in developed settings. It has been postulated that delay in diagnosis is common in developed settings. We reviewed all the cases of leprosy seen at a major tertiary referral centre between 1999 and 2013 and demonstrated that delay in diagnosis is common, especially when patients present with symptoms of leprosy reactions rather than classical symptoms, such as hypo-pigmented hypo-aesthetic skin lesions and neuropathy.
Leprosy remains an important global health concern with approximately 220 000 new cases diagnosed annually. In Australia, the disease continues to be reported with an average of 10 new diagnoses annually, predominately in migrants from endemic areas, but also sporadically within indigenous communities. Cases have also been reported in short-term travellers to endemic areas, indicating that leprosy should be considered in the differential diagnosis of any person with exposure to an endemic area to prevent delayed diagnosis.

Little has been published about the diagnosis and management of leprosy in developed settings. There are a few case reports which have demonstrated that delayed diagnosis occurs and that this delay could be due to a lack of physician awareness and knowledge about leprosy presentations. As a major tertiary referral centre for infectious diseases and tropical medicine, we conducted a retrospective analysis of leprosy cases seen at our institute over a 15-year period in order to examine for delay in diagnosis and analyse factors associated with delay. We have also briefly reviewed the diagnosis of leprosy and leprosy reactions to assist clinicians with its identification.

Our case series involved a search of Victoria’s iPatient management system to identify patients treated at our institution with leprosy as a listed diagnosis between 1999 and 2013. These cases were reviewed and diagnostic and treatment data gathered.

The review identified 30 possible patients of whom 16 had been treated for leprosy. The 14 patients excluded were either subsequently shown on investigation not to have leprosy or had been previously treated for leprosy and had no signs of active disease. Information about these cases is summarised in Table 1. All patients were migrants from endemic areas. One patient had lepromatous leprosy, three had tuberculoid leprosy and 12 had a borderline form. Eleven patients presented primarily with typical skin disease, four with predominantly neurological symptoms and one with non-typical skin disease. Seven patients were diagnosed with a leprosy reaction (four patients a type 1 reaction, three patients a type 2 reaction) either at presentation or after treatment commenced. Delay in diagnosis was clearly demonstrated in six cases where patients were treated for an erroneous alternative diagnosis prior to the diagnosis of leprosy. Patients who presented with symptoms of leprosy reactions rather than classical symptoms of hypopigmented, hypo-aesthetic skin lesions were particularly vulnerable. Of great concern is the high incidence of permanent disability (four out of six patients) where diagnosis was delayed.

In the cases of delayed diagnosis, failure to recognise the symptoms of a leprosy reaction or attributing traditional leprosy symptoms to other chronic disease were the common issues identified. Three patients presented with leprosy reactions that were not recognised and alternative treatment commenced. Two of these patients had acute onset neuropathic pain and skin oedema (type 1 reaction). In one case, ulnar nerve entrapment was diagnosed, and a cubital tunnel decompression was performed, which was complicated by chronic wound ulceration. In the other case, painful oedematous facial skin lesions were considered more consistent with cutaneous larvae migrans. The third patient had skin findings of erythema nodosum leprosum (ENL) (type 2 reaction) that were diagnosed as neurofibromatosis.

The other cases of delay occurred due to lack of identification of traditional leprosy symptoms and attributing these symptoms to other chronic medical conditions. In two cases, skin changes were not recognised and associated neuropathy was attributed to type II diabetes and lumbar radiculopathy, respectively, rather than leprosy. The third case had traditional skin changes and neuropathy. A biopsy was taken, but no acid-fast bacilli stain or leprosy polymerase chain reaction performed. Granulomatous changes were seen, and treatment with steroids for sarcoidosis commenced. It was only because of treatment failure that the case was revisited and leprosy changes identified.

*Mycobacterium leprae* infects the skin and peripheral nerves resulting in chronic inflammation and neuropathy. It is a slow growing infection with an incubation period of up to 12 years, and disease progression can be slow. The diagnosis of leprosy is made on the basis of clinical, microbiological and histopathological findings. Hypo-pigmented or reddish skin lesions with central hypo-aesthesia are the most common presenting finding, but some patients will present primarily with neuropathy. Biopsy demonstrates either granulomatous inflammation or foamy macrophages containing acid-fast bacilli. Polymerase chain reaction is increasingly available, and should be requested on all biopsy specimens to assist in diagnostic confirmation.

The clinical spectrum of leprosy is most commonly classified according to the Ridley–Jopling scale, which classifies disease on a spectrum based on host immunological response and bacillary load. At one extreme, those with tuberculoid leprosy have a strong T-helper cell type 1 (Th1) immune response leading to control of bacterial replication and spread. Histopathology demonstrates well demarcated granulomas, and few, if any, visualised organisms. At the other extreme, lepromatous leprosy is characterised by an absence of a specific T cell response.

**Funding:** None.

**Conflict of interest:** None.
Table 1 Demographic and key clinical information for reviewed cases of leprosy

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at diagnosis (years)</th>
<th>Sex</th>
<th>Country of exposure</th>
<th>Time between emigration and diagnosis (years)</th>
<th>Ridley–Jopling classification</th>
<th>Major presenting symptom</th>
<th>Initial diagnosis</th>
<th>Leprosy reaction and timing</th>
<th>Residual disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>M</td>
<td>Philippines</td>
<td>5</td>
<td>TT</td>
<td>Hypopigmented hypo-aesthetic skin lesion(s)</td>
<td>Leprosy</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>F</td>
<td>Sri Lanka</td>
<td>7</td>
<td>TT</td>
<td>Hypopigmented hypo-aesthetic skin lesion(s)</td>
<td>Leprosy</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>M</td>
<td>Sri Lanka</td>
<td>9</td>
<td>TT</td>
<td>Hypopigmented hypo-aesthetic skin lesion(s)</td>
<td>Leprosy</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>F</td>
<td>Sri Lanka</td>
<td>8</td>
<td>BB</td>
<td>Multiple painful skin nodules</td>
<td>Neurofibromatosis</td>
<td>Type 2 at presentation and diagnosis of leprosy, multiple recurrences</td>
<td>Bilateral hand weakness (finger abduction)</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>M</td>
<td>East Timor</td>
<td>6</td>
<td>LL</td>
<td>Hypopigmented hypo-aesthetic skin lesion(s)</td>
<td>Lumbar radiculopathy</td>
<td>Type 2 resulting in presentation and diagnosis of leprosy, multiple recurrences</td>
<td>Hypogonadism secondary to testicular infiltration.</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>M</td>
<td>Sudan/Kenya</td>
<td>1</td>
<td>BL</td>
<td>Hypopigmented hypo-aesthetic skin lesion(s)</td>
<td>Leprosy</td>
<td>Nil</td>
<td>Lower limb neuropathic pain</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>M</td>
<td>Sri Lanka</td>
<td>1</td>
<td>BT</td>
<td>Hypopigmented hypo-aesthetic skin lesion(s)</td>
<td>Leprosy</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>F</td>
<td>Sri Lanka</td>
<td>3</td>
<td>BT</td>
<td>Hypopigmented hypo-aesthetic skin lesion during pregnancy</td>
<td>Leprosy</td>
<td>Type 1 3 weeks into treatment</td>
<td>Nil</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>M</td>
<td>India</td>
<td>3</td>
<td>BT</td>
<td>Hypopigmented hypo-aesthetic skin lesion(s)</td>
<td>Leprosy</td>
<td>Type 1 22 weeks into treatment</td>
<td>Nil</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>M</td>
<td>India</td>
<td>3</td>
<td>BT</td>
<td>Pain and numbness left ulnar nerve distribution</td>
<td>Ulnar nerve impingement</td>
<td>Type 1 at presentation</td>
<td>Right hand weakness (finger abduction)</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>F</td>
<td>Sudan/Ethiopia</td>
<td>&lt;1</td>
<td>BT</td>
<td>Multiple hypo pigmented skin lesions, right elbow/hand pain with numbness</td>
<td>Leprosy</td>
<td>Type 1 at presentation with relapse 8 months into treatment</td>
<td>Bilateral hand and foot paresthesias, right hand weakness and neuropathic pain</td>
</tr>
<tr>
<td>12</td>
<td>55</td>
<td>M</td>
<td>Indonesia</td>
<td>6</td>
<td>BT</td>
<td>Hypopigmented hypo-aesthetic skin lesion(s)</td>
<td>Sarcoidosis</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>13</td>
<td>20</td>
<td>M</td>
<td>Kenya</td>
<td>1</td>
<td>BT</td>
<td>Firm linear mass medial left arm</td>
<td>Leprosy</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>14</td>
<td>29</td>
<td>M</td>
<td>India</td>
<td>&lt;1</td>
<td>BT</td>
<td>Hypopigmented hypo-aesthetic skin lesion(s)</td>
<td>Leprosy</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>15</td>
<td>73</td>
<td>M</td>
<td>Sri Lanka</td>
<td>1.5</td>
<td>BL</td>
<td>Bilateral hand weakness</td>
<td>Diabetic neuropathy</td>
<td>Type 2 on starting treatment with multiple recurrences</td>
<td>Permanent bilateral hand weakness</td>
</tr>
<tr>
<td>16</td>
<td>37</td>
<td>F</td>
<td>Sudan</td>
<td>4</td>
<td>BT</td>
<td>Hypopigmented hypo-aesthetic skin lesion(s)</td>
<td>Cutaneous larvae migrans</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

BB, borderline leprosy; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous leprosy; TT, tuberculoid leprosy.
resulting in uncontrolled bacillary proliferation typically leading to multiple skin lesions and extensive infiltration of the skin and nerves. Histopathology demonstrates foamy macrophages filled with many bacilli, few T-cells and a lack of organised granulomatous inflammation. The immune response to this form of disease is still poorly understood with features seen suggesting either a weak T-helper cell type 2 (Th2) response or T-cell deletion with permanent removal of T-cells specific for leprosy antigens from circulation. There are three borderline forms (borderline tuberculoid, borderline leprosy and borderline lepromatous) each of which show transitional features between the two extremes. These forms can be unstable and are more likely to have associated reactions.

Leprosy reactions are immunological reactions that can occur at any time before, during or after, treatment. These reactions are defined as either type 1 or type 2 reactions. Type 1 downgrading reactions can be associated with slow transition towards the lepromatous pole caused by diminishing cell mediated immunity. This is usually seen with relapsed leprosy or where treatment compliance has been poor. Type 1 reversal reactions occur where T-cell mediated immunity increases rapidly and disease shifts towards the tuberculoid pole with accelerated granulomatous inflammation. In type 1 reversal reactions, patients present with rapidly deteriorating neurology associated with neuritis and oedema of skin lesions. New lesions can also appear during these reactions. In contrast, type 2 reactions produce the syndrome ENL, which is thought to be caused by circulating immune complexes (type III hypersensitivity reaction). This typically results in a systemic illness, with manifestations, including multiple painful red skin nodules, neuritis, systemic symptoms of fever and lethargy, iritis, lymphadenitis, arthritis, orchitis and/or proteinuria. Patients can experience either reaction, but ENL reactions occur exclusively in patients near the lepromatous end of the spectrum. Both type 1 and type 2 reactions can be severe and may be the presenting symptoms of leprosy in some patients. Treatment of both leprosy and leprosy reactions is generally through WHO guidelines, except that in Australia patients with non-tuberculoid leprosy are generally treated for 2 years rather than 12 months because of lack of clear evidence that the shorter regimen is equally efficacious.

This case series highlights the importance of considering leprosy in the differential diagnosis of patients from endemic countries who present with skin changes or neuropathy. Even in non-endemic areas where cases occur infrequently, a reminder of the traditional symptoms of leprosy and leprosy reactions is important to avoid missed diagnosis. In particular, it is important to understand that while leprosy infection is generally slowly progressive, leprosy reactions are common, frequently are a reason for presentation and result in rapid progression of neurology and permanent disability. Making a timely diagnosis of leprosy reactions and commencing management (generally with prednisolone initially) is critical to minimising long-term disability. Of note, recurrent or recalcitrant reactions should be managed in specialised centres.

Leprosy must be considered as a diagnosis in all patients with skin changes and neurology from endemic areas even if their last exposure is likely to be many years ago. A biopsy or referral to a specialist for further evaluation should be performed. Failure to diagnose promptly and treat leprosy can result in increased morbidity and permanent disability. The case where diabetic neuropathy delayed the diagnosis is of particular importance as the rates of lifestyle diseases in endemic countries are increasing, and this style of presentation may become more common. Additionally, not only does leprosy continue to be diagnosed in Australia, but case rates may rise as migration from endemic areas increases.
Who really knows their patients’ penicillin adverse drug reaction status? A cross-sectional survey

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Key words
patient safety, penicillin, antimicrobial stewardship, adverse drug reaction.

Abstract
This cross-sectional survey of patients with adverse drug reactions (ADR) to penicillin and their treating doctor, nurse and pharmacist was undertaken to identify the extent of healthcare workers (HCW) awareness of their patients’ ADR, and antibiotic use in hospital. There were 23 (38%) doctors, 53 (87%) nurses and 40 (66%) pharmacists who were aware of their patient’s penicillin ADR, despite more than half of their patients receiving antibiotics. Interventions encouraging ‘double checking’ may improve antibiovigilance.

In a busy hospital, it is necessary for each treating healthcare team to be informed about their patients’ current medications and drug allergies. This is of particular relevance to patients with an adverse drug reaction (ADR) to penicillin who are prescribed antibiotics. We observed that many healthcare workers (HCW) were not aware of their patients’ ADR status and hypothesised that this may be a potential target for interventions to reduce medication errors.

A cross-sectional survey of patients with ADR to penicillin and their treating doctor, nurse and pharmacist was undertaken over a 4-week period. The study was conducted in a 640-bed, tertiary referral hospital in Melbourne, Australia. All hospitalised adult patients on 13 wards in the hospital were eligible to participate, comprising of medical, surgical, obstetric and gynaecological, coronary care and intensive care wards. The paediatric and psychiatry wards were excluded. The study was approved by Monash Health Human Research Ethics Committee. Consent was obtained from all patients prior to being interviewed about their penicillin ADR status.

Patients were classified as having an ADR to penicillin if during their interview they reported a past allergy or ADR to penicillin, or if they had ‘penicillin’ documented in the allergy/ADR section of the medication chart. Our study did not endeavour to confirm the nature and type of the patients’ reaction to penicillin through skin testing or other means, but rather utilised the information available to the HCW in our hospital.

For all patients with an ADR to penicillin, the current treating junior medical officer (26% interns, 49% residents and 25% registrars), ward pharmacist and treating nurse were interviewed on the same day.

Data collected included: whether they were aware if their patient had experienced any previous reactions to penicillin; whether they had directly taken an ADR history; whether they were aware if their patient was receiving antibiotic treatment and the antibiotic classes received. HCWs were deemed to be aware of their patients’ penicillin ADR status when their response to the question ‘are you aware if this patient has experienced any previous reactions to penicillin?’ was ‘yes.’

Statistical analysis was done using the IBM SPSS Statistics Data Editor (IBM, Armonk, NY, USA). P values for comparisons between groups were calculated using chi-squared or Fisher’s exact tests (where values were less than 5).

A total of 1054 patients was approached and 959 (90.1%) were able to give a history. Of these patients, 61
had a penicillin ADR: 52 (history and documentation), 2 (history only) and 7 (documentation only).

For each of the 61 patients with a penicillin ADR, their treating doctor, nurse and pharmacist were interviewed (total of 183 HCW interviews).

Seven (11%) doctors, 17 (28%) nurses and 18 (29%) pharmacists took an ADR history directly from their patient, the most common reason given for not taking a direct history was that ‘someone else had already done it’ (68%).

Twenty-three (38%) doctors, 53 (87%) nurses and 40 (66%) pharmacists were aware their patient had a penicillin ADR (Fig. 1). Pharmacists and nurses were more likely to be aware of their patients’ penicillin ADR than doctors, ($P = 0.004$ and $<0.001$ respectively).

Ten patients (16.4%) with a penicillin ADR, reported ADR to other antimicrobials. Thirty-four (56%) patients with a penicillin ADR were receiving antibiotics. Of these 34 patients receiving antibiotics, 5 (8%) received penicillins, 13 (21%) cephalosporins and 2 (3%) carbapenems; of these patients, the treating doctors were aware of the patient’s ADR in 3 (60%), 6 (46%) and 0 (0%) respectively.

Of the five patients with a history of penicillin ADR who were receiving penicillins, three (60%) developed an ADR, only one of which was consistent with their previous reaction to penicillin (Table 1). Only one of these patients described an ADR to another antimicrobial agent; however, this was not a beta-lactam. Out of the five patients receiving penicillin, three reported that their previous reaction to penicillin occurred over 10 years ago, additionally none of the past reactions was reported to have occurred within the first hour of penicillin administration. It is also important to consider that four out of the five patients receiving penicillin were considered to be immunosuppressed.

On questioning the reason for penicillin administration in patients with a history of penicillin ADR, two doctors confirmed that the decision was deliberate, with the therapeutic value of penicillin considered to be greater than the risks associated with a potential ADR. One was a medication error whereby the doctor prescribed a penicillin without realising that the patient had a penicillin ADR. In the final two cases, the cause was not able to be determined as the doctor reported that the reason was ‘unknown’.

The most remarkable finding of our study was that 23% of doctors, nurses or pharmacists took an ADR history directly from the patient they were caring for, despite over half of their patients actively receiving antibiotics. This may be responsible for the HCW poor awareness of their patients’ history of ADR to penicillin. This lack of awareness may have contributed to the inadvertent administration of penicillin to patients with a history of an ADR to penicillin. This finding is consistent with the current evidence, which identifies the

![Figure 1](image1.png) Healthcare worker knowledge of their patients’ penicillin allergies and antibiotic use while in hospital. ( ), Aware patient is allergic to penicillin; ( ), aware of whether the patient is receiving antibiotics or not.

Table 1 Patients with a penicillin ADR who received penicillin

<table>
<thead>
<tr>
<th>Details</th>
<th>Previous ADR</th>
<th>Time since ADR</th>
<th>Significant past medical history</th>
<th>Immunosuppressive medications</th>
<th>Antibiotic received</th>
<th>Penicillin reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vomiting</td>
<td>1 day</td>
<td>1 Year</td>
<td>ESRF, T2DM, IHD, AF, HTN</td>
<td>None</td>
<td>Piperacillin/tazobactam</td>
</tr>
<tr>
<td>2</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Breast cancer, encephalomyelitis</td>
<td>None</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>3</td>
<td>Angioedema</td>
<td>1 day</td>
<td>&gt;10 Years</td>
<td>COPD, AF, HTN</td>
<td>Prednisolone 5-mg PO daily</td>
<td>Piperacillin/tazobactam No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Rash</td>
<td>1 day</td>
<td>&gt;10 Years</td>
<td>T2DM, HTN, CKI, MSSA bacteraemia</td>
<td>None</td>
<td>Flucloxacillin No reaction</td>
</tr>
<tr>
<td>5</td>
<td>Vomiting</td>
<td>1 day</td>
<td>&gt;10 Years</td>
<td>Lung cancer</td>
<td>None</td>
<td>Ticarcillin/clavulanate Rash</td>
</tr>
</tbody>
</table>

ADR, adverse drug reaction; AF, atrial fibrillation; CKI, chronic kidney impairment; COPD, chronic obstructive pulmonary disease; ESRF, end-stage renal failure; HTN, hypertension; IHD, ischaemic heart disease; MSSA, meticillin-sensitive Staphylococcus aureus; PO, per oral; T2DM, type 2 diabetes mellitus.
contribution of human error to the risk of patient adverse events.1,2

In some cases, doctors may elect to re-challenge a patient who reports a penicillin ADR with penicillin-based antibiotics, based on a risk assessment elicited from knowledge of the ADR history and type and severity of infections.3,4 While we did not explore in detail the cognitive rationale of clinicians who prescribed penicillin in those with a history of a penicillin ADR, the majority of these patients were immunocompromised. It is therefore a possibility that the administration of penicillin-based drugs may have been critical with an alternative agent representing an inferior option.

A key limitation of our study was that we did not determine the accuracy of a patient’s ADR status. In many institutions (such as ours), skin testing is not widely available, hence it is not possible to verify which patients had ‘true allergy’ through skin testing. Three patients with a history of ADR to penicillin developed only mild ADR when they received penicillin. Only one patient developed a reaction to penicillin that was consistent with the previous ADR described. Given the nature of the penicillin ADR reported, it is unlikely that they were true allergies.5 Similarly, in 2013, the hospital’s pharmacy records demonstrate that 38 patients with a documented ADR to penicillin received penicillin, only three of whom developed an ADR. The frequent reporting of an ADR that is not consistent with a true allergy may result in the most suitable medication being avoided.

The aim of our study was to determine if HCWs caring for their patients verified the ADR history and were aware of their patients’ ADR status in a real life, real time situation. HCW poor awareness of their patients’ ADR status may relate to the fact that few HCW (23%) took a direct history from their patient. There is a great reliance on previously documented, as well as the ‘handover’ of, information from other HCW, despite inter-professional communication having been frequently identified as a vulnerable component of the care process.6,7

Our study has identified a weak link in the first step of the antibiotic prescribing chain. Future research in preventing error around penicillin allergy could be directed towards encouraging verification by the HCW at the bedside, so as to ‘double check’ a patient is not being prescribed an inappropriate medication.

References

LETTERS TO THE EDITOR
Clinical-scientific notes

Restrictive cardiomyopathy as a result of endomyocardial fibrosis from hypereosinophilia

A 52-year-old woman from Austria, on honeymoon in Queensland, Australia, presented to the Gold Coast University Hospital with hypotension and New York Heart Association class IV symptoms of heart failure. She reported a week-long history of progressively worsening shortness of breath and lethargy. Her medical history was significant for a T-cell lymphoma diagnosed in 2011 and initially treated with photopheresis. She was...
subsequently treated with a combination of doxyrubicin and cyclophosphamide between May and November 2013.

Physical examination of the patient revealed a blood pressure of 90/60 mm Hg, a regular heart rate of 110 b.p.m., jugular venous pressure elevated at 7 cm and an audible third heart sound. Examination of the respiratory system found bilateral pleural effusions. Abdominal exam revealed the presence of ascites. Her chest X-ray revealed a normal-sized heart and confirmed bilateral pleural effusions. Her electrocardiogram exhibited a left ventricular hypertrophic pattern, while her blood tests showed haemoglobin 119 g/L, haematocrit 0.37, mean cell volume 83 fl, white cell count $32.4 \times 10^9/L$, eosinophils $1.30 \times 10^9/L$, lymphocytes $18.49 \times 10^9/L$ and neutrophils $9.08 \times 10^9/L$.

The systolic function of both ventricles was found to be normal at echocardiography, but there was severe diastolic dysfunction with restrictive physiology. Valvular function was normal, however, the apex of the left ventricle was thickened with an apical mass filling nearly half the ventricle (Fig. 1a,b). A cardiac magnetic resonance imaging (MRI) was performed that showed endomyocardial fibrosis, which primarily involved the apical left ventricle with an associated large apical thrombus (Fig. 1c,d).

Bone marrow trephine biopsy showed normocellular marrow without fibrosis and with marked eosinophilia. Morphology and flow cytometry were suggestive of low-level marrow involvement with a mature T-cell lymphoproliferative disorder.

Based on the above findings, a diagnosis of restrictive cardiomyopathy from endomyocardial fibrosis secondary to hypereosinophilia was made. Although a diagnosis of eosinophilic infiltration is best made on cardiac biopsy, in our case, the clinical picture and the highly suggestive imaging findings were considered adequate to make the diagnosis of endomyocardial fibrosis. The hypereosinophilia likely occurred in the setting of her known T-cell lymphoma.

During her initial hospital course she was treated with steroids to suppress the hypereosinophilia, diuretics for her left ventricular failure and anticoagulation for the apical thrombus. She was treated and clinically stabilised and thereafter she flew back to Austria to resume chemotherapy.

In 1936, Loeffler described two cases of patients with congestive cardiac failure and severe blood eosinophilia, a condition that he named ‘fibroplastic parietal endocarditis with blood eosinophilia’.

The cardiac tissue damaging potential of eosinophils is attributed to its protein granule content, notably the eosinophil major protein and the eosinophil cationic protein. Cardiac involvement generally occurs in three stages: (i) an early acute necrotic stage with eosinophilic infiltration producing micro-abscesses; (ii) a thrombotic stage that affects the mural endocardium and results in endocardial thickening; and (iii) a late fibrotic stage that may affect the valves and chordae resulting in restrictive cardiomyopathy and valvulopathy.

There are no available data on the incidence of eosinophilic endomyocardial disease in patients with T-cell
lymphomas. There was no report of any cardiac abnormality among the 42 patients with peripheral T-cell lymphomas (of whom five had associated hypereosinophilia) in a study by Greer et al.,4 while Monsuez et al. had reported only two cases of eosinophilic endomyocardial disease out of 200 patients treated for non-Hodgkin lymphoma over a 4-year period.5

Echocardiography plays an initial role in diagnosing endomyocardial fibrosis, although MRI is fast emerging as an invaluable diagnostic tool by allowing a more comprehensive characterisation of heart involvement.6

In the case of our patient, echocardiography and MRI were both useful in reaching a diagnosis of endomyocardial fibrosis. Although her prognosis at this stage is not clear, she was successfully stabilised in our hospital and was able to fly back home to Austria for further management of her hypereosinophilia and T-cell lymphoma.

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References


Olmesartan-induced enteropathy

Olmesartan is an angiotensin II receptor antagonist with a long half-life that is used widely for the management of hypertension. Diarrhoea is a common side-effect and an indication for ceasing olmesartan.1 Sprue-like enteropathy is a rarely reported side-effect of olmesartan with only a few case reports identified to date. We report a case of sprue-like enteropathy induced by olmesartan.

A 75-year-old woman was referred for assessment of chronic diarrhoea, anorexia and weight loss that had commenced 8 weeks earlier. Her medical history included hypertension and she had commenced olmesartan 6 months prior to her onset of symptoms. Physical examination was remarkable only for muscle wasting without weakness. C-reactive protein, liver function tests and thyroid function test were normal. Faecal analysis was unremarkable. Coeliac serology (deaminitated antigliaden antibody) was negative. A gastroscopy and colonoscopy were unremarkable and biopsies of the duodenum revealed unsuspected total duodenal villous atrophy with prominent intraepithelial lymphocystosis (Fig. 1A). Colonic biopsies were normal.

Despite a confirmed, strict gluten-free diet, the patient’s condition was worse at 3-month follow up with progressive weight loss and ongoing daily diarrhoea. Human leucocyte antigen DQ2 (HLADQ2) was positive, but HLADQ8 was negative; repeat coeliac serology was negative and a repeat duodenal biopsy revealed no improvement. Additional tests for Whipple disease and Giardia were negative.

The diagnosis of olmesartan-related sprue-like enteropathy was considered. The drug was ceased and the patient resumed a normal diet without gluten restriction. Within 1 month, the patient had a normal bowel action and within 3 months, the weight improved to her
baseline. A repeat duodenal biopsy at 3 months was remarkably normal (Fig. 1B).

Drug-induced sprue-like enteropathy must be considered in the differential diagnosis of patients presenting with diarrhoea, weight loss and unexplained ‘coeliac-like’ changes in the duodenal mucosa. Olmesartan has been recently recognised as an important cause of drug-induced sprue-like enteropathy. In 2012, Rubio-Tapia et al. reported on 22 patients with severe sprue-like enteropathy associated with olmesartan. The median age of the patients was 69.5 years and the majority were prescribed a dose of 40 mg of olmesartan. Intestinal biopsies taken during gastroscopy showed severe villous atrophy with lymphocytic changes. Coeliac serology antibodies were negative and a gluten-free diet was not helpful. Histological recovery of the duodenum after discontinuation of olmesartan was confirmed in all 18 patients approximately 18 months later. Similar cases have since been reported and a systematic review published in 2014 identified 54 patients with olmesartan-induced enteropathy.

The causes of drug-induced diarrhoea are diverse and include acid suppression, infectious pathogens affecting water and electrolyte transport and drug-induced hypomotility or hypermotility among others. The mechanisms underlying olmesartan-associated enteropathy are unknown. One proposed mechanism is that the enteropathy is due to a cell-mediated immune response that results in damage to the small intestinal brush border. The long delay between onset of olmesartan therapy and the development of diarrhoea (and enteropathy) suggests that the reaction is unlikely to be a type I hypersensitivity response. In addition, angiotensin receptor blockers (ARB) have been suggested to have inhibitory effects on transforming growth factor, which maintains gut homeostasis. However, this effect does not explain why sprue-like enteropathy has only been seen with olmesartan and at present, other ARB do not appear to carry an increased risk of enteropathy. Moreover, the recent systematic review suggests a possible role for genetics in olmesartan-induced enteropathy including a high prevalence of the HLADQ2 or HLADQ8 halotype in the majority of patients.

Therefore, in the patient with unexplained diarrhoea and weight loss after commencement of olmesartan, the rare possibility of drug-mediated sprue-like enteropathy should be considered. It is important to note that the product information documents for olmesartan-containing products have recently been updated by the Therapeutic Goods Administration with a precaution for sprue-like enteropathy.

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References

Acute adrenal failure due to bilateral adrenal haemorrhage associated with lupus anticoagulant antibodies

A 57-year-old woman presented with fever and tachycardia. Two weeks prior to presentation she had suffered an unprovoked pulmonary embolus and deep vein thrombosis and had commenced treatment with enoxaparin. Her medical history was notable for severe epilepsy and a cerebellar tumour excised in childhood, which had left her cognitively and functionally impaired, necessitating full-time care.

On examination, she was found to be febrile at 39°C, tachypnoeic and tachycardic at 125 bpm with a blood pressure of 145/71. She was drowsy with a Glasgow Coma Scale of 13 from a baseline of 14. Left flank tenderness without peritonism was noted on examination. On diagnostic work-up, full blood examination showed haemoglobin concentration of 118 g/L, a platelet count of 83 × 10⁹/L and a normal total white cell count and differential. C-reactive protein was elevated at 218 mg/L and a full septic work-up was unremarkable. Serum sodium was normal, potassium was low at 2.8 mmol/L and urea and creatinine were elevated at 11.3 and 139 mmol/L respectively. Liver and thyroid function were normal, as was serum calcium concentration. The clotting profile in the presence of low-molecular-weight heparin (LMWH) showed an activated partial thromboplastin time (APTT) of 73, with a raised fibrinogen 9.9 and a normal INR. She was treated empirically for occult sepsis and received intravenous hydration. Over the next 48 h, there was no clinical improvement and further deterioration in her conscious state despite broadening of the antibiotic spectrum.

Both a steady down trend in haemoglobin to 81 g/L without overt haemorrhage or haemolysis, and the suspicion of an unidentified septic focus, prompted abdominal and pelvic contrast computed tomography. This demonstrated large bilateral adrenal haemorrhages (Fig. 1) and an extensive left iliopsoas haematoma. Intravenous dexamethasone was promptly administered and a marked improvement in her conscious state was observed over the following 12 h. A 6-am serum cortisol was significantly low at 23 nmol/L.

The clotting profile from the previous admission was then reviewed. This had shown a prolonged APTT, in the absence of LMWH, which did not correct with plasma mixing. Further testing during the current admission revealed grossly prolonged Russell’s venom viper and kaolin clotting times. Taken together with a positive Staclot-LA clotting assay that indicated lupus anticoagulant was strongly present, a diagnosis of underlying antiphospholipid syndrome (APS) was highly likely. Further immunological testing was not pursued as, in view of the extensive haemorrhages and coexistent thromboses, the decision was made to palliate her.

In the past 25 years, several case reports and two case series have described the association of APS with acute adrenal failure as a result of adrenal haemorrhagic infarction.1-5 APS is a thrombotic disease of the arterial and venous systems due to antiphospholipid antibodies that target phospholipid-binding plasma proteins such as B2-glycoprotein. These antibodies can be detected by their paradoxical prolonging effect on clotting assays, and this is the basis of the lupus anticoagulant test. Detection of specific antibodies, namely anti-cardiolipin and anti-beta2-glycoprotein, is by direct enzyme-linked immunosorbent assay.

It is proposed that adrenal vein thrombosis leads to adrenal haemorrhage in APS, and this is also thought true for more common precipitants such as sepsis and surgery.1-5 Haemorrhage following venous thrombosis may be explained by the organisation of the adrenal vasculature.3 The arterial supply travelling down through the cortex abruptly forms its capillary network at the junction of the zona reticularis and the medulla. Thrombosis in the medullary vein may lead to a sudden increase in pressure in the capillary network and disrupt these small non-muscular vessels. Anticoagulant therapy, as was present in this case, is a predisposing factor.6

Acute adrenal failure resulting from adrenal haemorrhage produces symptoms and signs less insidious than those of autoimmune adrenalitis.3 Abdominal pain, hypotension and fever are the three most common presenting symptoms of adrenal haemorrhage in the setting of APS.1,2 Although fever and abdominal pain were present in the case described, hypotension and shock were not observed. Tachycardia and continuous intravenous fluids were likely compensating for a reduction in circulating volume, which was implied by pre-renal failure. Indeed, other similar case reports describe arterial hypotension being delayed by up to 7 days after presentation with other symptoms such as abdominal pain.2

Relating back to the anatomy of adrenal haemorrhage it seems plausible that the most peripheral cortical layer, the zona glomerulosa, is affected last. Thus, the sequelae of mineralocorticoid depletion; reduced circulating volume and electrolyte imbalances, particularly hyponatraemia, may be delayed. Indeed, one case report of APS presenting with adrenal failure found that while the patient was cortisol deficient at presentation, the

Abbreviations: APPT, activated partial thromboplastin time; APS, antiphospholipid syndrome; LMWH, low molecular weight heparin.

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plasma aldosterone concentration was at the lower limit of normal but declined with time.²

In conclusion, patients with diagnosed APS or with a history of unprovoked thrombosis, who present with symptoms of adrenal failure with or without hypotension should be evaluated for adrenal haemorrhage. Furthermore, the occurrence of adrenal haemorrhage in the absence of typical precipitants should raise the suspicion of APS.

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References


General correspondence

‘Formalising the form?’: safety and quality concerns with not for resuscitation documentation

I read with interest Levinson and colleagues’ timely article with regard to variations in not for resuscitation (NFR) forms across five Victorian health services.¹

This is an important issue relating to the provision of high-quality end-of-life care (EOLC). Quality EOLC has become increasingly relevant in the current public health environment that is under pressure from an increasing and ageing population and rising costs of healthcare; alongside increasing patient autonomy in decision-making, and awareness of persisting use of aggressive, potentially futile and inappropriate treatments.²–⁴ In light of recent evidence, palliative care has developed a more prominent and assertive role in providing quality EOLC as patients and healthcare professionals strive towards a common goal of death with dignity and freedom from suffering.⁵

Where does the NFR form fit into the picture? Clarification and documentation of an NFR order features consistently in the literature as a key quality EOLC indicator, as does involvement of the patient, or persons responsible, in the decision-making process.⁷ Whether the NFR order requires the consent of the patient or persons responsible, however, varies across Australian jurisdictions, but Victorian law is clear in that the ultimate authority lies with the responsible clinician.⁸,⁹ The NFR order is a critical communication tool to avoid unnecessary, inappropriate or unwanted interventions for patients at the end of life.¹⁰

Fig. 1. Computed tomography demonstrating bilateral adrenal haemorrhages.

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Levinson and colleagues’ research is supported by previous studies that demonstrate significant non-uniformity in NFR policies and documentation in Australian hospitals.11 This is a real safety and quality issue given the importance of the NFR form in communicating this sensitive decision. Studies have shown that standardised operating forms do improve the documentation of the NFR decision, and therefore, they are arguably particularly relevant in our health system where healthcare providers often work at several different sites.12,13 The authors also raise the concern that the multiple existing variations of the NFR form can result in confusion as to whether the purpose of the NFR form is to communicate the decision-making process, the NFR order or both. This ambiguity ties into another quality issue – the actual utilisation of the form. Perhaps another useful study would be an audit of how the forms are actually completed.14 I informally examined 20 NFR forms in my hospital across oncology, renal, general medicine and general surgery units. Not one form had been completed as required. Aspects that were missing ranged from ‘diagnosis’ to ‘person responsible for decision’ to ‘persons involved’. One reason for this may in fact be the lack of clarity and uniformity in the structure and the purpose of the NFR forms. Ultimately, an imperfectly used form defeats the purpose of a perfectly designed form. The authors’ proposed strategy of a uniform two-stage process of documentation that encompasses and elucidates the decision-making pathway and the NFR order is a worthwhile consideration in order to improve this aspect of EOLC.

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The following errors were published on pages 1154 and 1155 of the editorial published in the December 2014 issue. A redundant abstract of the article was wrongly published as the first paragraph in the print version with an author affiliation that is not current. These errors have been amended in the online version.

We regret any inconvenience and confusion caused by these errors.
Instructions for Authors

AIMS AND SCOPE

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