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EDITOR'S NOTE

This is the second in a series of three editorials discussing the utility of the medical colleges in 2017. In the first, I suggested that medical colleges were becoming increasingly anachronistic and proposed some roles that colleges might assume if they were to serve a purpose other than guild-husbandry. In this follow-up editorial, Professor John Kolbe, a past President of the Royal Australasian College of Physicians, addresses the issues I raised and outlines the way in which he believes medical colleges can and do contribute to a wider social purpose.

Des Gorman,
IMJ Editor (Editorials)

EDITORIALS

Medical colleges: whose purpose, if any, do they serve?
A response

In his deliberately provocative but nevertheless thought-provoking lead editorial, Professor Gorman could be perceived as blaming all the misdemeanours undertaken and tolerated by the medical profession, and all the ills of modern healthcare provision, on the inabilities of medical colleges to address these issues adequately. He even goes so far as to demonstrate Godwin’s Law: ironically, originally formulated to reduce the incidence of inappropriate hyperbolic comparisons. While Gorman does quite correctly allocate a level of obligation to other groups, he does not ascribe to them the same level of responsibility as he does to medical colleges. This is despite the fact that these other groups may have the legislative powers, political influence and other ‘levers’ to address these issues, while colleges often do not. Perhaps colleges should be flattered that they are considered so influential, carry such moral authority and have the wherewithal to address these issues of gargantuan proportions. Ah, that this was indeed the case. In reality the colleges are but one, and at times a small part, in the complex behemoth that is modern healthcare. Many of the technologic, social, economic and political changes which are taking place in health and society are outside the current sphere of influence of the college. Even in post-graduate medical education, the training environment is complex and other cultures may exert as much if not more influence on the trainee than the college. The challenge for modern colleges is to define and assert clearly and unambiguously their roles and then deliver on these in a way that benefits patients and the community. In defining this role, I would encourage the colleges to be aspirational; to seek and secure roles well beyond those that they currently assume. George Bernard Shaw said: ‘the reasonable man adapts himself to the world: the unreasonable one persists in trying to adapt the world to himself. Therefore, all progress depends on the unreasonable man’. Gorman is exhorting members of colleges to be more ‘unreasonable’ – on this point I wholeheartedly agree with him. This is very similar to the concept of ‘disruptive innovation’ outlined by Derek Bell in the closing plenary address on quality, safety and value in healthcare at the recent Royal Australasian College of Physicians (RACP) Annual Scientific Congress.

It is not my intention that this article descend into a point-scoring exercise and semantic arguments, as to do so would trivialise the important question raised by Gorman: ‘Medical colleges – whose purpose, if any, do they serve?’ In addressing this question, I do not wish to be perceived as a ‘denier’ of the fact colleges have not always done all they could have, or been as proactive as they could and should have, in relation to certain issues; the ‘passive bystander’ argument of Gorman does have credence. The question is whether lessons have been learned and whether colleges are performing better. In the case of the RACP, I believe we are and hope to provide evidence for this contention. I will respond to some of the specific issues raised by Gorman, leaving my colleagues to address other aspects of the question posed.

Gorman provided a brief synopsis of the history of the UK colleges. While it is important to understand the origins of colleges, to suggest that our origins as guilds means that colleges are simply self-serving organisations ignores a great deal of evidence to the contrary. Being of the same
generation as Gorman, I too was an avid reader of the works of Ivan Illich, including ‘Medical Nemesis’. However, to suggest that colleges used ‘community service-type platforms’ merely to advance their own causes, is an unreasonably cynical and a somewhat disingenuous interpretation of the writings of ‘the Prophet of Cuernavaca’. In the remainder of this article, I will focus on the present and the future, although by doing so run the risk of diminishing the enormous significance of previous actions by medical colleges that have profoundly affected the health of millions. For example, based on research conducted by Professor (Sir) Richard Doll and colleagues, the Royal College of Physicians’ statement on cigarette smoking as a risk for development of lung cancer changed the smoking habits of society, brought about legislative changes and undoubtedly saved the life of millions.3 Sadly, it is necessary that the RACP advocacy on tobacco control continues to this day.

As repeatedly demonstrated within and outside the profession, colleges are a ‘soft target’ for critics. Detractors take perverse delight in referring to colleges as “old boys’ clubs”. The reality is quite different; the RACP membership is neither old nor dominantly ‘boys’. The RACP has 24,291 members; 16,507 fellows and 7,784 trainees. Of the fellows, 45% are <50 years and 34% female. Of trainees, 57% are female. All colleges, including our own, need to reflect on whether their deeds and actions and the resultant public perception make them vulnerable to such accusations and portrayals. The Earl of Chesterfield said: ‘Advice is seldom welcome; and those who want it most always like it the least’. Our college needs to be able to take advice and accept criticism. However, there are also obligations on the critics; their criticism should be informed, well-intentioned, constructive, given in the best interest of the college and always provided in a collegial fashion.

‘Hominum servire saluti – to serve the health of our people’ is the motto of the RACP. In the cases of the RACP (and the Royal Australasian College of Surgeons (RACS)), it is the college of rather than the college for; a very important distinction I believe. In relation to the particular characteristics of a profession by Brandeis referred to by Gorman, the RACP (and the RACS) would seem to meet all three requirements. First, the major role of the RACP is education; specifically vocational training and continuing professional development. Second, the college’s engagement in advocacy and other activities (which will be discussed below) and reflected in the motto, indicates that the college is striving to act ‘largely for (the benefit of) others and not merely for (itself)’. Third, the RACP made the decision some time ago that it would not engage in discussions or negotiations regarding the remuneration or working conditions of specialists. These philosophies are contained in the Tripartite (RACP, RACS and Royal College of Physicians and Surgeons of Canada (RCPSG)) statement on professionalism and is reflected in the Professional Qualities Curriculum and Supporting Physicians Professionalism and Performance framework.

The major role of the college is education: this is reflected in budget allocation, the staffing in the college and in levels of fellow engagement. While our college has provided trainees and fellows with excellent clinical knowledge and technical skills, the major change in the past 10–15 years has been the additional emphasis on the non-medical expert domains of the Professional Qualities Curriculum and Supporting Physicians Professionalism and Performance. The college will discharges a substantial portion of its social contract by ensuring that all physicians have, and maintain throughout their professional career, the requisite knowledge, skills and behaviours required of a modern physician. These now include a focus on continuous quality improvement, patient safety and provision of quality health care with the elimination of waste. Furthermore, these physicians are willing to be appraised to ensure they possess these qualities and are committed to improving their performance continuously – the concept of ‘demonstrable professionalism’. In doing so, they, in partnership with the college, are providing reassurance to the community (and regulators) that all physicians are ‘good enough’.6

Form should indeed follow function. While this is certainly not how the college structure came about, there has been major progress in the last decade to address a governance structure that had grown incrementally and was not fit for contemporary purpose. The major activities of the college are now reflected in college-wide committees for education, fellowship, finance, policy and advocacy and research. The various specialties within the broad church of the RACP are now more equitably represented on the College Board: the concept of ‘Specialists. Together’. At the most recent Annual General Meeting, a motion was passed that will allow a smaller (read less cumbersome) board, which will be less overtly representative and more skills based. It will continue to include non-fellows who bring additional but very valuable skills. This should allow the board to focus better on strategic issues. However, one could also argue that we still have a long way to go in the efficient and effective functioning of the college. Does the RACP really need almost 300 committees to allow it to function? Are all of these committees fulfilling their roles? In an ideal world, all college committees would be effective and efficient decision-making bodies that could reflect on their annual performance with a degree of satisfaction in the knowledge that they had ‘made a real difference’. Surely this is not unreasonable when one considers that it costs on
average $1000 for each member of a committee to attend each and every face-to-face meeting.

The relationship between the college and the specialty societies is an ongoing issue but one that is important for the long-term viability of both parties. Somewhat ironically, this issue was the reason for my involvement in the college. As President of the Thoracic Society of Australia and New Zealand, and thus as a member and subsequently Chair of the (then) Specialties Board, I recognised the critical importance of this, at times fraught, relationship. This is a maturing and mutually dependent relationship. The college cannot and does not wish to compete with the specialty societies in areas such as specialty-specific medical education to fellows. However, the college does have an important role in relation to the broader domains of professionalism, a role that it has been developing and expanding over the last few years. While it is the college education programme that has been accredited, cooperation and collaboration have existed for some time in the area of vocational education. However, there are much greater opportunities for joint activity, as exemplified by recent advocacy activities. Another example of the more collaborative nature of the relationship between the college and the specialty societies, and one that extends beyond training, is the contribution of specialty societies to EVOLVE.

Gorman challenges the need for individual medical colleges and suggests alternative structures based on international models. Any discussion of this needs to bear in mind that RACP is already a very ‘broad church’, much broader than other Australasian colleges; only RACS comes close. This has tremendous advantages but also presents challenges. There is no doubt that the RCPSC is a highly functional and effective organisation. It is undoubtedly the leader in vocational/post-graduate medical education. While this may relate to some extent to ‘scale’, I believe it is less due to college structure than due to the employment of the college of fellows with educational expertise on substantive contracts and who are then able to devote considerable time and effort to the Royal College. The Academy of Medicine in Hong Kong is an umbrella organisation. We already have such organisations: the Committee of Presidents of Medical Colleges in Australia and the Committee of Medical Colleges in New Zealand. These committees do provide the opportunity for interaction and dialogue between colleges. However, this interaction sometimes demonstrates the very different philosophical approaches taken by colleges. While these committees also provide a conduit to other important stakeholders, they remain in the category of ‘unrealised potential’. The medical colleges of Australasia have not been successful in developing and presenting a common approach to important health issues. As regards the issue of cooperation between colleges, the RACP has taken the view that a ‘coalition of the willing’ is preferable to ‘forced marriages’. The Tripartite Alliance (RACP, RACS and RCPSC) formally established in 2011 has been a tremendous success with progress on medical education and broad professional issues, that would have not been possible by any of the individual colleges. This limited alliance allowed the development of clear short and medium term goals with consequent tangible outcomes. This success is reflected in the fact that two other Australasian colleges have joined what is now called the Tri-Nations Alliance.

Although we both possess Australian ancestry, Des Gorman and I reside in New Zealand. How does New Zealand fare in this organisation? Is it overwhelmed by the bigger partner? Would New Zealand be better served, as Gorman suggests, by having stand-alone New Zealand colleges? Personally, I am in no doubt that New Zealand and New Zealand members benefit enormously by being part of an Australasian organisation. The depth and breadth of talent, the economies of scale and the ability to learn from each other have produced educational, advocacy and other outcomes that would have been impossible for a stand-alone New Zealand college. New Zealand’s nationality has been ‘recognised’ within the college governance structure. This does not mean that New Zealanders are not at times frustrated by what they perceive as undue focus on Australian issues, but I think they accept this state of affairs with grudging good grace (most of the time at least). The evidence indicates the New Zealanders ‘punch above their weight’ in the functioning of the college. It is somewhat ironic that the responses to Gorman’s article are by a New Zealand-based recent RACS President and a New Zealand based recent RACP President – and that the current RACP President-Elect is a New Zealand-based physician.

It is perhaps the ultimate cliché to say that ‘trainees are the future of our College’. As a result of a motion passed at the 2012 Annual General Meeting, trainees became members of the college with voting rights, this representing the greatest change in the membership of the college in its (then) almost 75-year history. Considering the tremendous contributions that trainees make and have made to the college, it is hard to believe that at the time the decision to give trainees voting rights generated so much debate. Trainees are now represented on virtually all college committees (including the board), yet, it was only a decade ago that serious concerns were expressed about how trainees might cope with issues of confidentiality and conflict of interest. My experience is that they deal with these issues at least as well as their more senior colleagues. This is future-proofing for the college – we have a large number of trainees who have
engaged with the college in a significant way, served on college committees and hopefully will remain engaged or re-engage in the future. It is just over 4 years since I stepped down as President. Although I have followed the actions of my successors with great interest and admiration, I now know personally fewer and fewer of the senior office-bearers in the college. Rather than bemoaning this fact, I see this as something very positive. The college is engaging new cohorts of members into leadership positions; broadening, refreshing and re-invigorating the college and its activities.

Although it has been the RACP policy for some time that fellows should undertake tasks that only fellows can do, and notwithstanding the enormous contribution by highly skilled, dedicated and diligent college staff, the RACP is still highly dependent on the pro-bono activities of fellows who have numerous competing demands on their time. There are also the issues of the reasonableness of expectations on these ‘volunteers’ and the extent to which this dependency has contributed to the lack of responsiveness of the college (in terms of a news cycle) to emerging issues and what sometimes appears to be an inbuilt stolidity of the college. The challenge is how best to harness the wisdom, experience, professionalism and goodwill of the fellows and trainees that constitute the membership of the RACP. Like the Immediate Past-President, I prefer the term ‘power of unity’ to that of economy of scale. However, is this situation sustainable? Should we not learn from the RCPSC experience and our own success in the appointment of fellows to the substantive roles of Director of Education and Dean, by appointing more fellows to paid positions for certain critical roles within the college? Should we be doing in policy and advocacy what has been so successful in education?

The college continues to progress from being reactive to more proactive on contemporary medical and social issues, establishing its credibility through thoughts, words and deeds. It has shown professional leadership particularly in relation to professional standards (partly through Supporting Physicians Performance and Professionalism) and on the issue of revalidation. It has engaged in debates on important, challenging and sometimes controversial, contemporary issues; producing carefully considered, evidence-based statements on the health benefits of work, the harms of alcohol, refugee health and well-being, the medical use of cannabis, to name but a few. The college is engaging much more in the debates regarding healthcare and healthcare delivery; the EVOLVE project is aimed at abolishing low-value treatments and interventions. The point is that the college is evermore outward looking and increasing assuming its right and proper role in societal debates and using its authority and influence for benefit of patients, the community and the profession. Our college has an important role now, but it is in the process of establishing the bases for even more important, relevant and expansive roles in the future.

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Advance Care Planning and Advance Care Directives: ideas whose time has passed?

End of life care is a perpetual issue of concern for community members and professional carers alike. There are many reasons for this, including the possibility that doctors have not always handled this aspect of care especially well and that both technical capacities and social attitudes are subject to change over time. Improvements in the capacity to treat serious illnesses and to prolong life, regardless of its quality, need to be reconciled with the availability of access to community-based caring facilities and the ability to respond to fears among elderly people about dementia, loneliness and dependency.

Vigorous public debates have often focused on three topics: statutory regulation of medical assistance with dying (which includes what is often referred to – sometimes misleadingly – as ‘euthanasia’), the introduction of legally enforceable Advance Care Directives (ACD) and universal application of formalised protocols for Advance Care Planning (ACP). Although opinions vary, each has acquired the appearance of a liberal cause and has been associated with pressure for legislative changes designed to enable or enforce certain practices. Statutory or common law provisions for ACD now exist in all states and territories, and national and state-based policies mandate the widespread implementation of ACP as part of routine care. Many healthcare services now incorporate into their programmes formal protocols that have to be followed for all patients, recording preferences and plans regarding end of life treatment, in many cases, included in checklists to be completed for every patient on a daily basis.

At first glance, all this appears unobjectionable. Surely, it is the right of all individuals to control when and how they die and what treatments they receive at the end of their lives? Surely, in a society that values individualistic style of American society, there are many cultures and religious perspectives in which ethical subjectivity is understood primarily – and primordially – in terms of relationships to, and responsibilities for, others.

As is so often the case in medicine, however, what is widely assumed to be obvious turns out to be more complicated than it first appears. Despite the powerful lobbying for euthanasia, lack of clarity persists about what is permissible under the current law and how best to respond to difficult cases. Similarly, both ACD and ACP rest on contested philosophical assumptions and are supported by evidence that is, at best, limited, in both quality and quantity. Two articles published in the Internal Medicine Journal have drawn attention to the complexity underlying the issues relating to ACD and ACP and suggest the need for fundamental rethinking.

In an article in the December 2016 issue, Denniss argues in favour of legislative clarification of ACD, but in the process exposes multiple major weaknesses in the underlying concept. In the April 2017 issue, Johnson et al. critically examine the underlying intentions of ACP and scrutinise the evidence available to support them.

A key common point stressed by both articles is that ACD and ACP share a central, basic assumption: that the protection and promotion of individual ‘autonomy’ is one of the key ethical objectives of medicine. In fact, Denniss goes as far as to state: ‘The moral underpinning of the ACD is the notion of autonomy. Everyone has the right to make decisions regarding their healthcare, an ethical principle which exists at the heart of modern medicine. Allowing competent adults to specify preferences to be enacted when their capacity is lost protects their self-determination during a state of powerlessness’.

Denniss goes on to summarise skillfully many of the challenges presented by the concept of ACD, including their frequent inability to provide specific guidance for treatment decisions or to respond to changing medical circumstances and patient and family preferences. In addition, she highlights problems associated with assessing competency and capacity. Nonetheless, she concludes that despite these deficiencies ACD ‘are ultimately the best solution that we currently have available’ to guide the management of end of life care.

Johnson et al. are a little more critical. Agreeing that ‘the conceptual justification for ACP is grounded in the principle of patient autonomy’ and the belief that following the wishes of patients regarding their end of life ‘may extend their autonomy into states of future incapacity’, they question whether ACP actually achieves this objective. In addition, they point out a second, equally fundamental purpose underlying ACP, and presumably ACD too: to enhance the quality of end of life care. The first purpose, they argue, requires ethical and philosophical scrutiny, while the second can be assessed directly through empirical evidence.

Despite frequent repetition of claims about the fundamental status of autonomy, especially in the US bioethical literature, this is by no means as clear as many assume. Indeed, there is much argument to show that the focus on autonomy is culturally specific and reflects the highly individualistic style of American society. There are many cultures and religious perspectives in which ethical subjectivity is understood primarily – and primordially –
Indeed, in some traditions ‘individualism’ is not just a secondary outcome of ethical relationships, but may even expose a pathological distortion of communal shared meaning. In these settings, it is the family, the community and the complex networks of care associated with them that are the proper locus of medical care.

From these points of view, the version of ‘autonomy’ represented in the modern tradition of bioethics and taken for granted in the everyday language of medicine may often missate the interests and concerns of many patients and thereby actually undermine effective and compassionate care. In the setting of end of life care, patients are often acutely aware of their embeddedness with family and loved ones, which often becomes a more important consideration than a need to retain ‘control’ of medical decision-making. In fact, as Johnson et al. point out, when patients talk about ‘control’ they often do not mean ‘control over individual decisions’, but rather ‘being respected, listened to and consistently having psychosocial concerns addressed’. In other words, the call for control refers less to technical decisions and check-boxes than it does to the broader ethical frameworks of care. This is, of course, not unfamiliar to palliative care practitioners, who have long recognised the critical role of careful, respectful, compassionate dialogue involving all the parties affected by an illness, including, in many cases, the professional carers themselves.

If the possibility is acknowledged that the driving intention of ACD and ACP – the maximisation of ‘autonomy’ – may be open to philosophical question, the apparent self-evidence of the appropriateness of such strategies may be less secure. In addition, the second question posed by Johnson et al. becomes more acutely relevant: Do ACD and ACP actually improve end of life care? Johnson et al. conclude that – at least in relation to ACP – there is in fact very little evidence to show that this is the case. From their detailed analysis of the multiple reviews of the extant data, they conclude that ACP may increase out of hospital care and compliance with patients’ wishes, but there is no convincing evidence of benefits regarding the management of patients’ physical symptoms, anxiety or depression, or caregiver strain. In general, they find that ‘there is no or limited or equivocal evidence to support efficacy of ACP’ in relation to the assumed end-points. Multiple other studies have come to similar conclusions regarding ACD.6,7

So where does this leave us? While it is too early to say that the era of ACD and ACP has passed, there are some important lessons here. First, it is important for us always to examine critically our ethical and philosophical assumptions. Frequent repetition of familiar attitudes or points of view is not sufficient to establish their validity. Second, certain practices may be widely adopted in medicine in the absence of empirical evidence of their effectiveness. Indeed, the history of medicine abounds with examples of ‘fashions’ that turned out not to improve patient care. Third, it can sometimes happen that the conversion of an undoubtedly sound idea – that patients and their families should be intimately included in the processes of decision-making and care – into rigid sets of protocols and formulae that are subject to legislation and formally mandated in clinical guidelines can distort original intentions and limit outcomes.

Of course, nothing in any of this suggests that doctors should not talk with their patients and families about the circumstances and possible implications of their illnesses and their values and preferences. As has always been the case, quality end of life care brings together a complex array of expert technical judgements, respectful communication, compassion and the building of trust, shared decision-making, and a secure, safe environment within which the most moving and difficult experiences can be negotiated. Rigid codification of approaches to treatment, compulsory directives and legislative enforcement of particular philosophical viewpoints may appear to provide protection to patients, but more often will threaten to undermine the creative openness from which clinical care has always derived its ethical power. What is needed is not increasingly elaborated and refined protocols and checklists, but a continuing awareness of the key role of open ethical dialogue in the practice of all aspects of clinical care.

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References

The benefit of exercise training in pulmonary hypertension: a clinical review

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Key words
pulmonary hypertension, exercise training, rehabilitation.

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Abstract
Pulmonary hypertension (PH) is a clinical condition characterised by raised pulmonary artery pressure, which results in increased right ventricular afterload and dyspnoea. This is accompanied by reduced exercise capacity, quality of life and, eventually, death. An increasing range of targeted medications has transformed the treatment of pulmonary arterial hypertension, a specific type of PH. Supervised exercise training is recommended as part of a multifaceted management plan for PH. However, many questions remain regarding how exercise training improves exercise capacity and quality of life. The optimal exercise regimen (frequency, timing, duration and intensity) also remains unclear. This review provides an update on the pathophysiology of exercise impairment in PH, suggests mechanisms by which exercise may improve symptoms and function and offers evidence-based recommendations regarding the frequency and intensity of an exercise programme for patients with PH.

Introduction
Pulmonary hypertension (PH) is a potentially life-threatening condition, defined by a mean resting pulmonary artery pressure (mPAP) ≥25 mm Hg measured by right heart catheterisation (RHC).1,2 PH is classified into five categories based on pathophysiology (Table 1). The estimated prevalence of PH in the Australian population is 326 cases per 100 000, with PH from left heart disease accounting for 250 cases per 100 000.3 While pulmonary arterial hypertension (PAH), a specific subgroup of PH (Table 1), only has an estimated prevalence of 26 cases per million, treatment for this condition has been recently revolutionised by the availability of targeted pharmacotherapies.

Regardless of aetiology, all types of PH may result in right ventricular (RV) remodelling, eventual RV failure (RVF) and death.6 Early stages of PH are often asymptomatic as the RV compensates by maintaining cardiac output (CO). However, with disease progression, patients develop worsening dyspnoea, fatigue, syncope and angina.7,8 Functional capacity is classified as outlined in Table 2.

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Recent advances in the pharmacological management of PAH have included an increasing range of prostanoids, endothelin receptor antagonists (ERA), phosphodiesterase (PDE) type-5 inhibitors and soluble guanylate cyclase (sGC) stimulators.9 These are now mostly funded by the Pharmaceutical Benefits Scheme (PBS) in Australia. This specific subtype of PH is defined by a mPAP ≥25 mm Hg with a pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and elevated pulmonary vascular resistance (PVR) > 3 Wood units (WU).1 Diagnosis of PAH also requires exclusion of significant lung disease and thromboembolic disease or other rare causes of pre-capillary PH.1 The management of patients with PAH is highly specialised and requires multi-disciplinary input from a range of healthcare professionals, including cardiologists, respiratory physicians, rheumatologists, rehabilitation physicians and cardio-pulmonary physiotherapists.7

Historically, exercise training (ET) in PH has not been recommended because of safety concerns.10 However, an increasing number of studies have demonstrated the benefit of ET on exercise capacity, peak oxygen capacity (peak VO2) and quality of life (QOL).11-14 Recent European guidelines recommend that supervised exercise training should be considered in physically de-conditioned patients with PAH that are clinically stable and on optimal pharmacological treatment (evidence Grade IIa, Level B).2
These patients.

tions regarding the frequency and intensity of exercise in function and provide evidence-based recommenda-
mechanisms by which exercise may improve symptoms exercise capacity and QOL in patients with PH, suggest
isms of improvement remain unclear.

1976 until February 2016 was performed. All English-
Search methods

A computerised literature search of the PubMed and PeDRO database using the key words ‘pulmonary hyperten-
and not powered to detect a change in 6MWD. Two of
this review.

Table 1 Classification of pulmonary hypertension3†

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension (PAH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic PAH</td>
</tr>
<tr>
<td>Heritable PAH</td>
</tr>
<tr>
<td>BMPR2, e.g. ALK-1, ENG, SMAD9, CAV1, KCNK3</td>
</tr>
<tr>
<td>Drug and toxin induced</td>
</tr>
<tr>
<td>Associated with connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis</td>
</tr>
<tr>
<td>1° Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis</td>
</tr>
<tr>
<td>1° Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td>2. Pulmonary hypertension because of left heart disease</td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
</tr>
<tr>
<td>Left ventricular diastolic dysfunction</td>
</tr>
<tr>
<td>Valvular disease</td>
</tr>
<tr>
<td>Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies</td>
</tr>
<tr>
<td>3. Pulmonary hypertension because of lung diseases and/or hypoxia</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
</tr>
<tr>
<td>Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
</tr>
<tr>
<td>Sleep-disordered breathing</td>
</tr>
<tr>
<td>Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td>Chronic exposure to high altitude</td>
</tr>
<tr>
<td>Developmental lung diseases</td>
</tr>
<tr>
<td>4. Chronic thromboembolic pulmonary hypertension (CTEPH)</td>
</tr>
<tr>
<td>5. Pulmonary hypertension with unclear multifactorial mechanisms</td>
</tr>
<tr>
<td>Haematologic disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy</td>
</tr>
<tr>
<td>Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangiopilomatosis</td>
</tr>
<tr>
<td>Metabolic disorders: glycogen storage disease, Gauchers disease, thyroid disorders</td>
</tr>
<tr>
<td>Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH</td>
</tr>
</tbody>
</table>

†5th WSPH Nice 2013. BMPR, bone morphogenic protein receptor type II; CAV1, caveolin-1; ENG, endoglin; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension.

However, the optimal duration, intensity, frequency and type of exercise for patients with PH15 and the mechanisms of improvement remain unclear.

This review paper will examine the benefit of ET on exercise capacity and QOL in patients with PH, suggest mechanisms by which exercise may improve symptoms and function and provide evidence-based recommendations regarding the frequency and intensity of exercise in these patients.

Search methods

The 18 published studies (Table 3) examining the effect of ET on PAH explored a wide range of exercise interventions, ranging from an inpatient rehabilitation programme to pure inspiratory muscle training.

Fifteen studies reported an improvement in 6-min walk distance (6MWD) post-exercise, which ranged from 32 ± 11 m (P = 0.0033)21 to 98 ± 61 m (P = 0.0001).17 Recent meta-analyses have concluded that ET improves 6MWD by 53.3–72.5 m in patients with PH (95% CI 39.5–99.1 m).11–13 The difference in 6MWD in the training compared to the control group in patients with PAH was 72.5 m (95% CI 46–99.1 m).11 This distance was greater than the minimum clinically significant difference (MCD) of 25–33 m.15 Interestingly, a meta-analysis of studies of PAH-specific medication reported a mean increase in 6MWD of 35.6 m (95% CI 27–44 m).36 These findings suggest that ET may result in an improvement in 6MWD at least as great as that achieved with pharmacotherapy. This is important given the low cost of ET and the low risk of side-effects. What is not known is whether the benefit of ET is limited to tests of exercise capacity or if ET improves RV function.

Three studies found no improvement in exercise capacity as measured by 6MWD.18,20,31 However, these studies were small (combined total of 44 participants) and not powered to detect a change in 6MWD. Two of these studies18,20 focused on cycling and lower limb

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<table>
<thead>
<tr>
<th>First author date of publication</th>
<th>Study design</th>
<th>Disease†</th>
<th>No. patients</th>
<th>WHO class</th>
<th>Type of exercise programme</th>
<th>Duration</th>
<th>Outcome measures</th>
<th>Effect of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mereles (2006)</td>
<td>RCT crossover</td>
<td>PH (PAH, CTEPH)</td>
<td>30</td>
<td>II–IV</td>
<td>Aerobic Strength Respiratory</td>
<td>3-week inpatient 12-week home programme</td>
<td>6MWD</td>
<td>Positive</td>
</tr>
<tr>
<td>Fox (2011)</td>
<td>Non-RCT cohort</td>
<td>PH (PAH, CTEPH)</td>
<td>22</td>
<td>II–III</td>
<td>Interval aerobic training Resistance training Home exercise</td>
<td>2-week x 12 weeks</td>
<td>6MWD</td>
<td>Positive</td>
</tr>
<tr>
<td>Grunig (2011)</td>
<td>Cohort</td>
<td>PH (PAH, CTEPH)</td>
<td>58</td>
<td>II–IV</td>
<td>Aerobic Strength Respiratory</td>
<td>3-week inpatient 12-week home programme</td>
<td>TTCW similar to treatment with medication only Survival similar to treatment with medication only</td>
<td>Positive</td>
</tr>
<tr>
<td>Grunig (2012)</td>
<td>Cohort</td>
<td>PH (PAH, CTEPH)</td>
<td>183</td>
<td>I–IV</td>
<td>Aerobic Strength Respiratory</td>
<td>3-week inpatient 12-week home programme</td>
<td>6MWD</td>
<td>Positive</td>
</tr>
<tr>
<td>Nagel (2012)</td>
<td>Cohort</td>
<td>CTEPH</td>
<td>35</td>
<td>II–IV</td>
<td>Aerobic Strength Respiratory</td>
<td>3-week inpatient 12-week home programme</td>
<td>6MWD</td>
<td>Positive</td>
</tr>
<tr>
<td>Grunig (2012)</td>
<td>Cohort</td>
<td>CTD-APAH</td>
<td>21</td>
<td>II–IV</td>
<td>Aerobic Strength Respiratory</td>
<td>3-week inpatient 12-week home programme</td>
<td>6MWD</td>
<td>Positive</td>
</tr>
<tr>
<td>First author date of publication</td>
<td>Study design</td>
<td>Disease†</td>
<td>No. patients</td>
<td>WHO class</td>
<td>Type of exercise programme</td>
<td>Duration</td>
<td>Outcome measures</td>
<td>Effect of exercise</td>
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<tr>
<td>Chan (2013)†²⁷</td>
<td>RCT</td>
<td>PAH</td>
<td>23</td>
<td>I–IV</td>
<td>Treadmill</td>
<td>2–3 week x 10 weeks</td>
<td>6MWD</td>
<td>56 ± 45 m</td>
</tr>
<tr>
<td>Ley (2013)†²⁸</td>
<td>RCT</td>
<td>PH (PAH) (CTEPH)</td>
<td>20</td>
<td>II–III</td>
<td>Aerobic Strength</td>
<td>3-week inpatient 12-week home programme</td>
<td>6MWD</td>
<td>91.4 ± 66 m</td>
</tr>
<tr>
<td>Weinstein (2013)†²⁹</td>
<td>RCT</td>
<td>PAH</td>
<td>24</td>
<td>I–IV</td>
<td>Aerobic</td>
<td>3-week x 10 weeks</td>
<td>Fatigue † Activity score † 6MWD</td>
<td>153 ± 44 m Exercise test duration † Not all patients had RHC Positive</td>
</tr>
<tr>
<td>Raskin (2014)¹⁰ included Review</td>
<td>Retrospective</td>
<td>PAH</td>
<td>23</td>
<td>II–IV</td>
<td>Lower limb endurance</td>
<td>2–3 week</td>
<td>not included in analysis 6MWD</td>
<td>81 ± 30 m TwPmo</td>
</tr>
<tr>
<td>Kabitz (2014)³⁰</td>
<td>Cohort</td>
<td>PAH</td>
<td>7</td>
<td>II–IV</td>
<td>Aerobic Strength Respiratory</td>
<td>3-week inpatient 12-week home programme</td>
<td>6MWD</td>
<td>53 ± 54 m</td>
</tr>
<tr>
<td>Ihle et al. (2014)³¹</td>
<td>Case series</td>
<td>PH</td>
<td>17</td>
<td>II–III</td>
<td>Strength Respiratory</td>
<td>Once per month Home programme (10 months)</td>
<td>No increase in 6MWD No change in QOL</td>
<td>Negative</td>
</tr>
<tr>
<td>Inagaki (2014)³²</td>
<td>Cohort</td>
<td>CTEPH</td>
<td>8</td>
<td>II–III</td>
<td>Walking Strength Respiratory</td>
<td>1 week x 12 weeks Home programme</td>
<td>6MWD</td>
<td>33.3 ± 25.1 m Quadriceps force</td>
</tr>
<tr>
<td>Saglam (2015)³³</td>
<td>RCT</td>
<td>PAH</td>
<td>20</td>
<td>II–III</td>
<td>Inspiratory muscle Training</td>
<td>30 min/day, daily x12 weeks home programme</td>
<td>MIP † MEP † 6MWD</td>
<td>150 m Fatigue † Peak VO2 † Cardiac index † mPAP † (by RHC) PVR † 6MWD † QOL</td>
</tr>
<tr>
<td>Ehiken (2016)³⁴</td>
<td>RCT</td>
<td>PAH</td>
<td>87</td>
<td>II–IV</td>
<td>Aerobic Strength Respiratory</td>
<td>3-week inpatient 12-week home programme</td>
<td>6MWD</td>
<td>56 ± 45 m</td>
</tr>
</tbody>
</table>

†Brackets indicate main PH subgroup recruited. CPET, cardiopulmonary exercise testing; CTEPH, chronic thromboembolic pulmonary hypertension; CT-APAH, connective tissue associated pulmonary arterial hypertension; CHD-APAH, congenital heart disease associated pulmonary arterial hypertension; FSS, fatigue severity scale; HAP, human activity scale; IPAH, idiopathic pulmonary arterial hypertension; MEP, mean expiratory pressure; MIP, mean inspiratory pressure; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; peak VO2, peak oxygen consumption; Pulm, pulmonary; pulm MRI, pulmonary magnetic resonance imaging; QOL, quality of life; RHC, right heart catheterisation; RCT, randomised controlled trial; SGRQ, St George respiratory questionnaire; TwPmo, twitch mouth pressure; TTCW, time to clinical worsening; 6MWD, 6-min walk distance.
strength training and did not include other types of endurance training, such as walking or respiratory muscle exercise. However, improvements in endurance, muscle capillarisation and oxidative enzymes\textsuperscript{18} and World Health Organization functional class\textsuperscript{26} were noted, suggesting that cycling and lower limb strength training may be beneficial. The remaining study only reported monthly supervision of participants during the exercise programme.\textsuperscript{31} Such infrequent supervision may not have encouraged sufficient participant motivation or adherence to the exercise regimen.

**The impact of exercise training on QOL**

Patients with PH have impaired sleep quality\textsuperscript{37,38} and reduced health-related quality of life (HR-QOL).\textsuperscript{37–42} This is especially seen in those with scleroderma-associated PAH.\textsuperscript{45} Reduction in HR-QOL was related to poor exercise capacity, symptoms of right heart failure (RHF), depression and anxiety.\textsuperscript{46} Interestingly, there was no reported significant association between HR-QOL and objective measures of resting haemodynamics (mPAP, PVR, cardiac index).\textsuperscript{40,42}

Seven studies have shown that ET was associated with improved QOL.\textsuperscript{17,22–27} Studies using the non-disease-specific Short Form-36 (SF-36) to assess QOL found ET improved physical scores,\textsuperscript{17,24,25} mental health,\textsuperscript{17,25} scores of vitality and general health perception and social functioning\textsuperscript{24,25} and appeared to lower pain scores.\textsuperscript{26}

Other studies have used PH-specific validated questionnaires, such as the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).\textsuperscript{43} Participants reported post-exercise improvements in energy, dyspnoea and mood,\textsuperscript{27} as measured with the CAMPHOR and SF-36. Decreased fatigue and by the Fatigue Severity Scale (a validated, Likert scale that measures patient fatigue), and higher levels of physical activity were also reported after ET.\textsuperscript{29} A recent meta-analysis concluded that exercise improved QOL with particular benefit on physical and social function.\textsuperscript{11}

While it appears that ET improves exercise capacity, QOL and physical and social function, the mechanism of how this occurs is not known. Possible mechanisms of improvement are discussed below.

**Mechanisms of improvement**

The following changes have been noted in patients with PH following ET:

**Improvement in peak oxygen consumption**

Peak oxygen consumption (VO\textsubscript{2}/kg) is the highest amount of oxygen consumed by an individual undergoing cardiopulmonary testing (CPET) and is a measure of aerobic capacity.\textsuperscript{44} Multiple small studies of ET have shown a benefit on peak oxygen consumption (VO\textsubscript{2}/kg)\textsuperscript{17,21,25–27,34} – possibly because of increased skeletal muscle capillary density.\textsuperscript{54}

**Change in skeletal muscle fibre type**

A small, non-randomised study of five patients with idiopathic PAH (iPAH) showed improved quadricep muscle function and alteration of fibre morphology on muscle biopsy to a less fatigable type (decrease in Type IIx and increase in Type I fibres).\textsuperscript{19}

A study of 19 patients with iPAH reported increased quadricep strength and endurance after a 12-week exercise programme involving cycling and quadriceps training. Muscle biopsy showed increased capillaries per muscle fibre and increased oxidative enzyme activity, particularly in the type 1 (slow twitch) fibres. These structural changes correlated with increased quadricep endurance.\textsuperscript{18}

**Improvement in cardiac function**

The effect of ET on cardiac function in humans is unknown. Animal studies suggested that ET may reduce RV end-diastolic pressure (RVEDP) and improve pulmonary artery remodelling.\textsuperscript{45} In rats with stable PH, ET increased RV myocyte capillarisation.\textsuperscript{46} These findings have yet to be demonstrated in humans. A meta-analysis of human studies reported an increase in peak exercise heart rate by 10 beats per min (95% CI 6–15 beats per min).\textsuperscript{12} When taken in conjunction with improved VO\textsubscript{2} max, this suggests an improvement in cardiac function following ET.

**Improvement in haemodynamics**

Despite improved clinical status, earlier studies did not show improved haemodynamics following ET as assessed by stress Doppler echocardiography.\textsuperscript{17,21} Subsequent analysis of data from pooled analyses found that ET reduced echo PA systolic pressure by 3.7 mmHg (95% CI −5.4 to −1.9).\textsuperscript{12} One small study using magnetic resonance imaging (MRI) found reduced peak velocity in the pulmonary artery and increased pulmonary blood volume post-ET.\textsuperscript{28} This suggested that haemodynamic parameters may improve following exercise.

The first study to measure the effect of ET on haemodynamics via RHC was recently published.\textsuperscript{14} This randomised controlled trial (RCT) examined the effect of an inpatient exercise prescription (previously described)\textsuperscript{17} in 87 participants with PAH or chronic thromboembolic PH (CTEPH). The intervention (ET) group underwent a 3-week inpatient programme followed by a 12–15-week
home-based exercise programme. The inpatient exercise protocol consisted of interval training with a bicycle ergometer for 10–25 min per day to maintain participants’ heart rate at 60–80% of maximal heart rate. The ET group also underwent 60 min of walking per day, 5 days per week. In addition, 30 min of respiratory training involving stretching and breathing techniques, such as pursed lip breathing and strengthening of respiratory muscles, and weight training (500–1000 g) of major muscle groups for 30 min was also undertaken 5 days per week. The protocol involved a minimum of 2 h of exercise per day, 5 days per week for the intervention (ET) group.

The home-based exercise programme given to the ET group after their 3-week inpatient stay consisted of aerobic exercise (bicycle ET on a supplied bicycle ergometer) at an intensity close to their target heart rate. They were advised to use the bicycle daily for a total of 15–30 min, 5 days per week. The exercise group was also asked to continue second daily respiratory exercise and resistance training with weights for 15–30 min. Participants were also asked to walk twice a week for a total of ≥120 min walking per week. The control group were able to do their usual activity, but did not have an ET programme prescribed.

The primary outcome measure, peak VO2, significantly increased in the ET group. Secondary outcome measures, such as cardiac index (CI), mPAP and PVR and exercise capacity and QOL, all improved post-ET. The improvement in haemodynamics suggested that ET may improve RV function. However, larger studies directly measuring haemodynamic parameters by RHC and measures of RV function (e.g. by cardiac MRI) are required to confirm these results.

**Evidence-based recommendations for exercise prescription**

All patients with PAH must be clinically stable and on optimal pharmacological agents prior to commencing any exercise training/rehabilitation.

**Frequency, duration and intensity of exercise**

The ideal timing, frequency, duration and intensity of exercise for the treatment of PH remain unclear. The most commonly used exercise prescription, as described above, is very intensive with regards to frequency, duration and type of exercise prescribed. All studies using this protocol showed significant gains in 6MWD in the ET group, varying from 67 ± 59 m ($P = 0.0001$) to 96 ± 61 m ($P = 0.0001$).

These impressive gains were probably because of the nature and intensity of the exercise programme (aerobic, strength training and respiratory muscle training), the close supervision that enhanced adherence with exercise and technical factors, such as the use of the correct technique for respiratory muscle exercises. While these studies reported impressive gains in 6MWD, the intensity and mode of rehabilitation (3 weeks, inpatient) suggest that these studies may not be widely generalisable to routine clinical practice.

Nine small studies have examined a variety of outpatient exercise programmes. The improvements in 6MWD were less, compared to the inpatient protocol (Fig. 1), suggesting that the benefit from the latter may have been because of the intensity of ET.

Given the above findings, it appears that ET should occur on at least 5 days per week, for at least 2 h per day. However, this may not be easily achievable because of logistics (staff availability, lack of patient transport, excessive travel time, limited healthcare resources, patient time commitments), lack of patient energy/motivation and inability to comply with this intensity. A more realistic programme of exercising two to three times per week for 1 h per session may still confer a benefit on distance walked, peak oxygen consumption, QOL, self-reported symptoms, fatigue and activity levels.

**Components of exercise training**

Studies reporting the largest increase in 6MWD usually included aerobic exercise, such as cycling or walking for endurance training, strength training using light weights and respiratory muscle exercises. However, these studies involved intensive inpatient programmes, so it remains unclear whether the type and frequency of exercise, or increased adherence because of daily supervision, was more important. It is also unknown how long the benefits of exercise training persisted following completion of the programme as long-term outcomes were only reported in one study. However, this small study of eight patients was probably inadequately powered to detect a difference at 12 months.

**Hydrotherapy**

To our knowledge, no studies have included hydrotherapy as a treatment modality. Although hydrotherapy is often used in rehabilitation programmes and is beneficial for many conditions, it is not recommended in patients with PH because of the potential effect of increased intra-thoracic pressure with water immersion as this could reduce RV function and increase RV pressure.
Safety and supervision of exercise training

The long-term safety of ET in patients with PH has been studied in an observational, uncontrolled study of 58 patients with class II–IV PH. Participants underwent 3 weeks of inpatient ET and 15 weeks of a home-based exercise programme. The primary outcome measure was time-to-clinical worsening (TTCW) and death. Secondary outcome measures were 6MWT, WHO functional class and QOL measures. There were no serious adverse events, such as syncope, arrhythmias, RHF or symptom progression. The authors reported a one- and two-year survival rate of 100% and 95%, respectively, suggesting that a supervised intensive exercise programme was safe. There were no additional adverse events when the cohort exercised unsupervised at home. There was an improvement in 6MWD (84 m ± 49 m, \( P < 0.001 \)), WHO functional class and QOL at Week 15 compared to baseline. However, as these outcomes (6MWT, WHO functional class and QOL) were not measured after 15 weeks, it was unclear if these benefits were sustained. Larger controlled studies with longer follow up are required to determine if ET confers a long-term benefit on morbidity and mortality.

A large study of 183 PAH patients also examined the safety of ET. Fourteen per cent of participants reported an adverse event, for example, pre-syncope, syncope and self-limiting supraventricular tachycardia. Given the potential for serious complications during exercise, all patients with PH undertaking ET should have access to experienced clinicians. All published studies have involved at least weekly supervision. We therefore suggest all patients with PAH be reviewed prior to commencing an exercise programme and undergo regular review. However, the benefits of ET probably outweigh the risks.

Barriers to exercise

Contraindications

Exercise is contraindicated in patients with PH who have unstable disease with evidence of RV decompensation, have clinical evidence of RHF, recent hospitalisation or are undergoing investigation for clinical deterioration. Other contraindications include a recent history of chest pain, palpitations, light headedness, dizziness or syncope on exertion. All patients with PH should obtain medical clearance from their treating physician prior to ET.

Physical and logistic difficulties

Patients with CTD-aPAH, particularly scleroderma, may find exercise difficult because of joint contractures and toe ulcers. In this case, the programme should focus on respiratory muscle strengthening or use of an arm ergometer. Although it can be difficult accessing experienced clinicians in rural and regional areas, this is being addressed by the establishment of regional PAH Clinics.

Conclusion

Exercise training in patients with PH appears to have significant benefits on endurance, peak oxygen consumption, haemodynamics and skeletal muscle function. The magnitude of improvement in 6MWD is similar to that seen with pharmacotherapy. All PH patients should undergo a thorough medical assessment prior to exercise and have access to experienced clinicians during the exercise period.
While an intensive inpatient ET programme has been shown to be beneficial, this is often not available. A less intensive outpatient programme may be more accessible, but its effectiveness requires further investigation. Components of a suitable exercise programme that require further investigation include strength training, aerobic/endurance training and respiratory muscle training. Despite these limitations, exercise training in PH has a good safety profile with few serious adverse effects and should be encouraged as part of a multi-disciplinary treatment programme.

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Orthostatic hypotension: pathophysiology, assessment, treatment and the paradox of supine hypertension

Peter Chisholm and Mahesan Anpalahan

Abstract

Both hypertension and orthostatic hypotension (OH) are strongly age-associated and are common management problems in older people. However, unlike hypertension, management of OH has unique challenges with few well-established treatments. Not infrequently, they both coexist, further compounding the management. This review provides comprehensive information on OH, including pathophysiology, diagnostic workup and treatment, with a view to provide a practical guide to its management. Special references are made to patients with supine hypertension and postprandial hypotension and older hypertensive patients.

Introduction

Orthostatic hypotension (OH) is a common clinical problem, especially in older people. Although it has been known since the early 20th century, a consensus definition of OH was not reached until 1996. The classic type of OH is defined as a sustained reduction in systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mmHg within 3 min of standing or head up tilt to an angle of 60 degrees with or without reproduction of symptoms. However, a SBP drop of ≥30 mmHg in those with hypertension (supine SBP ≥160) and an absolute standing SBP <90 mmHg in those with low baseline blood pressure (BP) may be appropriate for the diagnosis of OH. Initial OH is defined as a transient drop in either systole ≥40 mmHg or a diastole ≥20 mmHg within 15 s of standing. Delayed OH, where haemodynamic changes occur after 3 min of orthostasis, may represent a mild or early autonomic dysfunction and may be confused with vasodepressive-type neurally mediated syncope.

The prevalence of OH has been variably reported, in part due to the age and comorbidities of the population. Prevalence between 9% and 34% has been reported in unselected community dwellers. The prevalence increases in aged care facilities and in acute hospitals, up to 50% and 41%, respectively. The comorbidities that have a particular influence on the prevalence of OH are neurodegenerative disorders, such as Parkinson disease (up to 58%), diabetes (up to 28%) and hypertension (up to 32%).

OH is an important risk factor for falls and syncope. It contributes to cerebrovascular and cardiovascular morbidity and mortality, even in those without pre-existing disease. It also has a clear association with all-cause mortality. Furthermore, it is associated with chronic kidney disease, cognitive impairment and prothrombotic state. The increased cardiovascular and cerebrovascular risk may be due to shared vascular risk factors, such as prevalent hypertension, including supine or nocturnal hypertension and diabetes mellitus. Acceleration of atherosclerosis mediated by the pulsatile haemodynamic stress due to fluctuations in BP has been proposed as another mechanism – the so-called Systemic Haemodynamic Atherosclerotic Syndrome.

Pathophysiology

Upright posture results in gravitational pooling of 500–1000 mL of blood in the capacitance vessels in the lower extremities and splanchnic circulation, resulting in decreased venous return, cardiac output and low BP. Pooling also promotes extravasation of plasma, further compromising venous return. These changes trigger baroreceptor-mediated autonomic, circulatory and
humoural compensatory responses, leading to increased heart rate (HR), peripheral resistance and venous return. The autonomic response results in sympathetic activation and parasympathetic inhibition. The humoural responses include the activation of the renin–angiotensin aldosterone system, antidiuretic hormone secretion and a decrease in serum atrial natriuretic peptide, resulting in the preservation of salt and water.

Due to these mechanisms, upright posture in a normal person does not result in major changes in BP other than for an initial transient drop. A normal response during orthostasis, depending on age, includes a transient drop in SBP (10–15 mmHg), a slight increase in DBP (5–10 mmHg) and compensatory tachycardia of up to 10–25 beats per minute. An exaggeration of this initial drop in BP is responsible for initial OH, which is due to a transient mismatch between cardiac output and peripheral resistance. It occurs during active standing as opposed to passive standing.

From a pathophysiological point of view, OH can be broadly categorised into neurogenic and non-neurogenic causes (Table 1, Fig. 1). Neurogenic OH is the most common type and virtually all cases of chronic OH without an identifiable cause could be managed as neurogenic OH. Neurodegenerative diseases are the main cause of central neurogenic OH, and diabetic neuropathy is the prototype for peripheral neurogenic OH. The non-neurogenic causes are usually acute and consist of miscellaneous disorders that are mostly cardiovascular, circulatory or medication related (Table 1). Physiological changes of ageing including decreased baroreceptor sensitivity and muscle pump activity, and impaired water homeostasis contribute to OH. However, advancing age in and of itself is not a cause of OH.

Assessment of OH

Patients usually present with symptoms of orthostatic intolerance, which are usually worse in the morning, during standing, physical activity and hot weather. Hot showers, meals and ingestion of alcohol often exacerbate symptoms. However, older patients may present with atypical symptoms such as confusion, fatigue or hanger pain. Symptoms of OH should be graded for assessment and to monitor progress.

Patients should rest supine for 5 min before baseline BP is recorded as BP is the least variable after 5 min of rest. Orthostatic stress should be administered for 3 min, or longer if delayed OH is suspected. Assessment can occur using the active stand method or head up tilt table testing, and some have recommended the latter. However, there is no clear evidence to support one over the other. Although the sit-to-stand technique is convenient and widely used, its diagnostic accuracy is not validated, and neither is supine to sit or squat to stand.

Intermittent BP measurement with digital or manual sphygmomanometry is most widely used. Non-invasive beat-to-beat technology has a far greater diagnostic yield, although it is unclear whether its routine use will improve patient outcomes. However, it is essential for diagnosing initial OH.

The recommended frequency of BP measurements varies between guidelines. As the nadir of BP drop occurs within 1 min, usually at 30 s, BP measurements should ideally occur at 30 s, 60 s and thereafter every minute. HR should be measured concurrently to help differentiate between neurogenic and non-neurogenic causes and others, such as postural tachycardia syndrome. A lack of HR response >10–15 per min suggests neurogenic OH, although autonomic testing would be required in milder cases. Age, the duration of supine rest and medications, such as beta blockers, are potential confounders when interpreting HR response.

Ambulatory blood pressure monitoring (ABPM) has an adjuvant diagnostic role in OH if patients can record posture and initiate manual recordings during symptoms. However, the principal application of ABPM in OH is for assessing nocturnal and supine hypertension and postprandial hypotension.

Treatment of OH

The aims of treating OH should be ameliorating symptoms and improving quality of life rather than achieving target BPs, with the expectation of reducing adverse clinical outcomes, such as falls and syncope. However, there is no evidence to suggest that these outcomes are affected by the treatment of OH, particularly pharmacological treatment.

Initial management should include screening for acute precipitants, such as culprit medications and hypovolaemia. Pharmacological therapy should always be coupled with non-pharmacological measures and only after the latter has been proved to be inadequate. Patient and carer education is paramount, and it is important to pay attention to concurrent supine hypertension.

Non-pharmacological management

Physical counter measures

Patients should be advised to stand slowly in stages to prevent sudden falls in BP. Bending forward when standing improves venous return by causing abdominal compression. It also improves cerebral perfusion by lowering the head to the level of the heart. Manoeuvres

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Table 1 Causes, features and treatment of orthostatic hypotension

<table>
<thead>
<tr>
<th>Cause of orthostatic hypotension</th>
<th>Clinical characteristics</th>
<th>Supportive diagnostic features</th>
<th>Special considerations for treatment</th>
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</thead>
<tbody>
<tr>
<td>Neurogenic</td>
<td></td>
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<tr>
<td>Parkinson disease</td>
<td>Bradykinesia, rest tremor, rigidity</td>
<td>Autonomic functional assessment: Mild cardiovagal and adrenergic abnormalities</td>
<td>Non-pharmacological and pharmacological management (see text)</td>
</tr>
<tr>
<td></td>
<td>Responsive to levodopa</td>
<td>TST: normal or distal anhidrosis</td>
<td>Droxidopa effective (Level 1 evidence)</td>
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<tr>
<td></td>
<td>Autonomic dysfunction is variable, usually a late feature, often aggravated by dopaminergic treatment</td>
<td>Cardiac MIBG-SPECT: impaired uptake</td>
<td>Domperidone as an adjunctive may be considered</td>
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<td>Plasma noradrenaline: supine normal but orthostatic response low</td>
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<td></td>
<td></td>
<td>MRI brain: usually normal</td>
<td></td>
</tr>
<tr>
<td>Multiple system atrophy (MSA)</td>
<td>Parkinsonian features with severe autonomic dysfunction</td>
<td>Autonomic functional assessment: Severe cardiovagal and adrenergic abnormalities</td>
<td>Non-pharmacological and pharmacological management (see text)</td>
</tr>
<tr>
<td></td>
<td>Poorly responsive to levodopa</td>
<td>TST: widespread anhidrosis</td>
<td>Droxidopa effective (Level 1 evidence)</td>
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<tr>
<td></td>
<td>Features of impaired coordination and pyramidal signs</td>
<td>Cardiac MIBG-SPECT: normal but can be abnormal in late stages</td>
<td>Clonidine effective for supine hypertension</td>
</tr>
<tr>
<td></td>
<td>Early stages can be difficult to differentiate from Parkinson disease, especially MSA-P (MSA with predominant parkinsonism)</td>
<td>Plasma noradrenaline: supine normal but orthostatic response low</td>
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<tr>
<td>Pure autonomic failure</td>
<td>Symptoms of severe autonomic failure without motor manifestations: neurogenic bladder and bowel, erectile dysfunction, anhidrosis</td>
<td>Autonomic functional assessment: Severe cardiovagal and adrenergic abnormalities</td>
<td>Non-pharmacological and pharmacological management (see text)</td>
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<td></td>
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<td>TST: widespread anhidrosis</td>
<td>Droxidopa effective (Level 1 evidence)</td>
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<td>Cardiac MIBG-SPECT: impaired uptake</td>
<td>Clonidine effective for supine hypertension</td>
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<td>Plasma noradrenaline: supine markedly reduced and orthostatic response low</td>
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<td></td>
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<td>MRI brain: atrophy of putamen, pons, middle cerebellar peduncle, and cerebellum</td>
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<tr>
<td>Dementia with Lewy bodies</td>
<td>Cognitive fluctuations</td>
<td>Autonomic functional assessment: Intermediate cardiovagal and adrenergic abnormalities (&lt; MSA but &gt; Parkinson disease)</td>
<td>Non-pharmacological and pharmacological management (see text)</td>
</tr>
<tr>
<td></td>
<td>Visual hallucinations</td>
<td>TST: distal anhidrosis</td>
<td>Non-pharmacological treatment may be affected by cognitive impairment</td>
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<td></td>
<td>Parkinsonism</td>
<td>Cardiac MIBG-SPECT: impaired uptake</td>
<td></td>
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<td></td>
<td>Impaired executive and visuospatial functions</td>
<td>MRI brain: normal non-specific atrophy</td>
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<tr>
<td></td>
<td>Sensitive to neuroleptics</td>
<td>SPECT brain: Occipital hypoperfusion</td>
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<tr>
<td></td>
<td>Autonomic dysfunction is a common and early feature</td>
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<tr>
<td>Diabetes</td>
<td>Autonomic symptoms usually include gastroparesis, altered bowel habit and erectile dysfunction, in the presence of longstanding diabetes</td>
<td>Autonomic functional assessment: Impaired cardiovagal and adrenergic response</td>
<td>Non-pharmacological and pharmacological management (see text)</td>
</tr>
<tr>
<td></td>
<td>Usually associated with polyneuropathy, particularly small fibre disease (symptoms of pain and burning of the toes and feet)</td>
<td>TST: distal anhidrosis, global anhidrosis in severe dysautonomia</td>
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<td></td>
<td>Charcot's arthropathy</td>
<td>Cardiac MIBG-SPECT: may have impaired uptake in severe autonomic dysfunction</td>
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<td>Plasma noradrenaline: Supine low and orthostatic response low</td>
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<tr>
<td>Cause of orthostatic hypotension</td>
<td>Clinical characteristics</td>
<td>Supportive diagnostic features</td>
<td>Special considerations for treatment</td>
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<tr>
<td>Neurogenic (continued)</td>
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<tr>
<td>Amyloidosis (familial and primary)</td>
<td>Generalised polyneuropathy with small fibre disease. Other organ involvement such as cardiac, renal etc.</td>
<td>Autonomic functional assessment: Impaired cardiovagal and adrenergic response Subcutaneous fat, gingival and rectal biopsies Blood and urine electrophoresis (for primary amyloidosis)</td>
<td>Non-pharmacological and pharmacological management (see text)</td>
</tr>
<tr>
<td>Dopamine beta hydroxylase deficiency</td>
<td>Onset of symptoms during childhood and early adulthood. Reduced exercise tolerance, ptosis, nasal stuffiness, intact sweating</td>
<td>Low plasma adrenaline Elevated plasma dopamine Genetic testing</td>
<td>Droxidopa is drug of choice</td>
</tr>
<tr>
<td>Autoimmune autonomic ganglionopathy</td>
<td>Features of severe pandysautonomia presenting acutely or subacutely</td>
<td>Ganglionic nicotinic acetylcholine receptor (nAChR) autoantibodies</td>
<td>Immunosuppressive therapy including plasma exchange IVlg</td>
</tr>
<tr>
<td>Hereditary sensory and autonomic neuropathies (especially type 3)</td>
<td>Absence of tears, pain sensitivity and lingual fungiform papillae, depressed pupillary reflexes</td>
<td>Genetic evaluation: splicing mutation in the leb kinase-associated protein gene Lack of axon flare following intradermal histamine</td>
<td>Non-pharmacological and pharmacological management (see text) In dysautonomic crisis: diazepam, clonidine, carbidopa, pregabalin may be used</td>
</tr>
<tr>
<td>Other peripheral neuropathies (alcohol, paraneoplastic, HIV, Guillain Barré syndrome)</td>
<td>Glove and stocking distribution of sensory loss Features of the primary disorder</td>
<td>Electrodiagnostic assessment: nerve conduction studies Paraneoplastic antibodies: anti-Hu etc.</td>
<td>Non-pharmacological and pharmacological management (see text) Plasma exchange, IVlg, immunosuppressive therapy (Guillain Barré Syndrome and paraneoplastic)</td>
</tr>
<tr>
<td>Spinal cord lesions/brain stem lesions</td>
<td>High spinal cord lesions are usually characterised by dysregulated sympathetic function and preserved parasympathetic function (variable blood pressure, reflex bradycardia)</td>
<td>MRI: to confirm level of lesion Plasma noradrenaline: usually low</td>
<td>Non-pharmacological and pharmacological management (see text)</td>
</tr>
<tr>
<td>Sjogren syndrome</td>
<td>Decreased lacrimal and salivary gland function</td>
<td>Tests for anti-Ro (SSA) and anti-La (SSB) antibodies</td>
<td>Non-pharmacological and pharmacological management (see text) Hydroxychloroquine Methotrexate Biologic agents</td>
</tr>
<tr>
<td>Non-neurogenic</td>
<td>Medication history Temporal association with introduction of medication</td>
<td>Orthostatic hypotension in the context of normal heart rate response to orthostasis No other evidence of autonomic dysfunction</td>
<td>Review of medications Consider substitution of offending agents</td>
</tr>
<tr>
<td>Medications (including vasodilators, diuretics, psychotropics)</td>
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<td></td>
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<tr>
<td>Volume depletion</td>
<td>Clinical signs of for volume loss</td>
<td>—</td>
<td>Optimise volume status</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>Clinical signs for congestive cardiac failure</td>
<td>Echocardiogram may be useful</td>
<td>Avoid fluoroquinolones and salt Nocturnal use of antihypertensives</td>
</tr>
</tbody>
</table>
that increase muscle contraction of the legs improve venous return, and examples include leg crossing, dorsiflexing the feet and squatting.\textsuperscript{33,34}

Compression stockings (waist-high with pressures of 40–60 mmHg at the ankle and 30–40 mmHg at the hip) have been shown to be effective in improving BP and symptoms; however, they are poorly tolerated.\textsuperscript{35} Abdominal binders are a possible alternative, which recruit blood from the splanchnic reservoir.\textsuperscript{36} Thromboembolic deterrent stockings are widely used, but there is only anecdotal evidence for their efficacy in mild OH.\textsuperscript{36}

Other measures

Elevating the head of the bed by 6–9 inches (approximately 15–20 cm) during sleep has been shown to be effective in small observational studies in autonomic failure.\textsuperscript{37} The proposed mechanism is a reduction in overnight diuresis and natriuresis due to reduced nocturnal BP and renal perfusion. However, the efficacy of this intervention has been challenged by a recent randomised controlled trial (RCT).\textsuperscript{38} This study, however, did not differentiate between the causes of OH, and inadequate hydration and possibly inadequate elevation of the bed too may have contributed to the negative result. Therefore, further studies are required to clarify its efficacy. In the interim, however, given its relative safety, it is recommended at least in those with autonomic failure.

Volume status can be optimised with intake of salt and water.\textsuperscript{39} Patients without contraindications should be encouraged to take 6–10 g of sodium chloride (1–2 teaspoons daily, 1–2 tablets TDS) and 1.5–2 L of fluid per day.\textsuperscript{40} A urinary sodium excretion > 170 mmol per day confirms adequate salt intake.\textsuperscript{31} A free water bolus has been shown to have an acute pressor effect: two 8-ounce glasses of water in rapid succession (480 mL) improves systolic BP by 20 mmHg.\textsuperscript{42}

Pharmacological management

Midodrine, an α\textsubscript{1} agonist, stimulates arterial and venous adrenoceptors.\textsuperscript{43} Its short half-life of 2–4 h allows it to be used as a short-term vasopressor when upright during the day, with little worsening of nocturnal hypertension. It is preferably taken before getting out of bed, around midday and mid-afternoon, in doses of 2.5–10 mg and is best avoided within 4 h of sleeping to prevent supine hypertension.\textsuperscript{43} It is generally well tolerated, with side effects that include urinary hesitancy, paraesthesia, pruritis and piloerection.\textsuperscript{44} It has been found in RCT to improve standing BP in neurogenic OH,\textsuperscript{45} although evidence for patient-relevant outcomes, such as improvement in symptoms or quality of life, is inconsistent.\textsuperscript{44,46} Currently, two trial results are pending regarding these outcomes.

Droxdopa is a noradrenaline prodrug with a short life of 2–3 h. It is not yet available in Australia but has been used in Japan for more than a decade and was recently approved in the United States for neurogenic OH. It improves BP as well as symptoms in neurogenic OH, including in dopamine β-hydroxylase deficiency, and is tolerated well.\textsuperscript{47} However, its efficacy is unclear in diabetes. The starting dose is 100 mg TDS and can be titrated up to a maximum of 1800 mg per day. It should be avoided within 5 h of bed time to avoid supine hypertension.\textsuperscript{45}

Fludrocortisone, a synthetic mineralocorticoid, acts by improving circulating blood volume and blood vessel sensitivity to pressor agents.\textsuperscript{48} Although it is suggested

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<tbody>
<tr>
<td>Non-neurogenic (continued)</td>
<td></td>
<td></td>
<td>May require pressor agents</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Malaise, anorexia, weight loss, fatigue, gastrointestinal symptoms</td>
<td>Synacthen test</td>
<td>Glucocorticoids and mineralocorticoids</td>
</tr>
<tr>
<td>Deconditioning</td>
<td>Severe physical deconditioning post-acute illness</td>
<td>Rehabilitation</td>
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as the first-line treatment in some guidelines, given salt and water retention and its long half-life, it may not be suitable for patients with heart failure and nocturnal hypertension. A dose >0.3 mg is usually associated with hypokalaemia and oedema, with little clinical benefit.

Pyridostigmine (up to 60 mg TDS), a cholinesterase inhibitor, has the advantage of not aggravating supine hypertension. However, its pressor effect is modest, and it is less well-tolerated due to gastrointestinal side effects.

Atomoxetine (18 mg daily), a noradrenaline reuptake inhibitor, has been shown to increase standing BP in a single-dose crossover trial, with improvement in BP and symptoms compared to midodrine and placebo. However, its long-term effects are not known.

Caffeine (250 mg or two cups of coffee per day) inhibits peripheral vasodilatation and thus increases standing BP. Dihydroergotamine may be considered in autonomic failure in patients without underlying vascular disease. In a recent study, in combination with caffeine, it was found to be effective in improving BP and symptoms in autonomic failure.

In appropriate patients, erythropoietic agents may be used. Non-steroidal anti-inflammatory drugs may be effective, although their side effect profile precludes their long-term use. There is limited evidence for the use of vasopressin (DDAVP), especially in those with polyuria, although its clinical utility is limited by hypotraemia. Yohimbine (an α2 antagonist) has also been shown to improve BP in autonomic failure in one study. There is anecdotal evidence for the use of dopamine antagonists, such as metoclopramide and domperidone, particularly for the latter in Parkinson disease. QT prolongation with domperidone and dyskinesia with metoclopramide are considerations.

Figure 1 Management algorithm for orthostatic hypotension. *See text. DBP, diastolic blood pressure; OH, orthostatic hypotension; SBP, systolic blood pressure.
OH in specific groups and situations

Supine and nocturnal hypertension

OH, especially neurogenic OH, is frequently associated with supine and nocturnal hypertension, and the severity of nocturnal hypertension correlates with the magnitude of OH. Approximately 50% with pure autonomic failure and multiple system atrophy (MSA) have supine hypertension defined as a SBP ≥150 mmHg and DBP ≥90 mmHg. The mechanisms of supine hypertension are unclear. Increased vascular resistance due to residual sympathetic activity has been suggested in patients with MSA. Serum angiotensin II levels have also been shown to be high in patients with supine hypertension despite low levels of renin.

The assessment of supine and nocturnal hypertension should be routine in chronic OH. Its presence limits treatment options as the treatment of one adversely affects the other. There is also evidence from cross-sectional data for its association with target organ damage, such as left ventricular hypertrophy and cerebrovascular disease. Therefore, there is a clinical imperative to diagnose nocturnal and supine hypertension. Supine hypertension can be easily diagnosed by measuring BP in the supine position, although it can be easily missed as BP in routine clinical practice is often measured only in the seated position. ABPM is better suited for this purpose as it provides greater insight into BP behaviour and treatment effects over 24 h.

Management of supine hypertension includes avoiding recumbency during the day, especially when using compression devices or pressor agents; sleeping with the head of the bed raised; taking carbohydrate-rich snacks at bedtime; and avoiding liquid within an hour of bedtime. Alcohol may be used in appropriate clinical circumstances. The judicious use of pressor agents for OH is an important aspect of managing supine hypertension (see pharmacological management).

If non-pharmacological measures are not successful, short-acting anti-hypertensive medications should be considered at bedtime. The cut off BP to start anti-hypertensive therapy has not been defined, and treatment decisions should be made on an individual basis. However, anti-hypertensive agents would generally be indicated if the nocturnal BP is >180/110. Although bed time dosing of BP medications is the most sensible approach to managing nocturnal hypertension in ambulant patients, these patients will be at a greater risk of OH during night time as a result, and therefore should be cautioned about night time movements. Angiotensin II receptor blockers may be used in preference to angiotensin-converting enzyme inhibitors in alignment with the pathophysiology of supine hypertension. Short-acting angiotensin-converting enzyme inhibitors (captopril), angiotensin II receptor blockers (losartan), calcium channel blockers (nifedipine), hydralazine, minoxidil, use of overnight glyceryl trinitrate patches (with removal 1 h before rising) and clonidine are generally recommended. Sildenafil (25 mg) has also been shown to be effective, and pindolol may be used as it may have limited impact on daytime OH due to its intrinsic sympathomimetic effect.

Postprandial hypotension

Postprandial hypotension is an important association of OH. It is generally defined as a fall in SBP greater than 20 mmHg or a drop of SBP <90 mmHg within 2 h of a meal. However, there is lack of consensus regarding this diagnostic criterion. The decrease in BP usually starts 15 min after a meal, peaks at 30–60 min and lasts for up to 2 h. In addition to dizziness, symptoms may include sleepiness, nausea and headache. Given the variability of the onset of haemodynamic changes, BP recordings at frequent intervals, at least every 30 min, are required for at least 90 min after a meal, and it is best achieved by ABPM. Management strategies include: small and frequent meals of low carbohydrate content; drinking water before and with meals; minimising alcohol intake; and using drugs such as caffeine (200–250 mg or two cups of coffee), acarbose (100 mg), guar gum (9 g), droxidopa (up to 1000 mg) and octreotide (50 μg subcutaneous).

Elderly hypertensive patients

OH is common in older hypertensive patients. The risk factors include poorly controlled hypertension, prescription of three or more anti-hypertensives and prescription of vasodilators and diuretics. However, transient OH after commencing anti-hypertensive medications is not uncommon in older people, and it usually does not require any intervention. The management of these patients is difficult as they are usually frail and have an increased risk of falls and functional impairment. Treatment requires balancing the risks of hypertension against the potential hypertensive effects of medications. Not infrequently, the common practice is to withdraw anti-hypertensive medications, but this can be counterproductive, resulting in the exacerbation of OH and falls. In this context, it is worth noting that the incidence of OH was significantly lower in the intensive BP treatment arm in the recent SPRINT trial. The prudent approach would be to control hypertension by carefully selecting appropriate anti-hypertensive...
medications, preferably short-acting agents.\(^5\) The timing of the medications may need to be staggered to accommodate patients’ functional needs and the 24-h BP profile.

## Conclusion

Although OH is a common clinical problem, many facets of this disorder remain poorly understood. Management often poses difficult challenges, with a limited evidence base to guide therapy. Many commonly recommended treatments have not been subjected to rigorous investigation, and only a few trials have concentrated on patients without autonomic failure. The clinical correlations, natural history and the long-term complications of initial OH are not known, although data suggest that delayed OH may not be as benign as once thought.\(^7\)

Proof of concept studies suggest a role for ABPM in OH, and this should be further explored in RCT. The clinical significance of brief but significant drops in BP and prolonged drops that do not meet the diagnostic threshold of OH is unclear.\(^2\) Furthermore, there is little or no evidence to inform what duration of BP drop should be considered as ‘sustained’ for diagnosing OH. The lack of a gold standard for diagnosis and poor reproducibility of BP measurements\(^3\) are significant limitations to compare and assess diagnostic protocols and efficacy of treatments. RCT with patient-relevant clinical outcomes, such as syncope, falls, quality of life and other hard vascular outcomes, as end-points are required.

## Acknowledgements

We acknowledge the contribution of Dr Harry Harianto, Eastern Health, Melbourne, for his help with the manuscript.

## References


Orthostatic hypotension


Hepatitis A to E: what’s new?
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Key words

Abstract
Viral hepatitis contributes to significant morbidity and mortality worldwide. While acute infection may be self-limiting, unrecognised chronic infection and under-utilisation of guideline-based approaches to therapy contribute to increasing rates of cirrhosis, hepatocellular carcinoma and death. Our aim was to review the current evidence for screening, diagnosis and treatment in hepatitis A to E. Evidence for this review was sourced from international and Australian guidelines and high-quality clinical trials. MEDLINE was searched using structured key word strategy and retrieved articles were reviewed methodically to inform a brief and up-to-date synopsis of hepatitis A to E. We share some of the recent developments in viral hepatitis, specifically the new therapies for hepatitis C. Direct-acting antiviral therapies are safe, well-tolerated and effective. Subsidies allow access for all Australians with most strains of hepatitis C. We outline evidence underpinning efficacy and safety of treatment for hepatitis B, while clarifying some of the nuances in the setting of pregnancy and immunosuppression. We provide a simplified concept to facilitate understanding of the five phases of hepatitis B; practical for real-world setting. Hepatitis A to E is a broad topic, not all aspects of these viruses can be covered in this short review. We provided suggestions for evidence based guidelines, which are a suitable supplement to this article.

Introduction
Viral hepatitis causes significant morbidity and mortality worldwide. While often self-limiting, it can lead to chronic infection, cirrhosis, hepatocellular carcinoma (HCC) and death. The aim of this review, is to provide a simple and up-to-date synopsis of hepatitis A to E. Understanding of pathogenesis, impact and therapeutics has all changed appreciably in the past few years. Changes have occurred specifically with (i) direct-acting antiviral (DAA) therapy for the treatment and cure of hepatitis C, (ii) evaluation and diagnoses of cirrhosis, and (iii) evaluation and treatment of hepatitis B in special settings, like pregnancy and immunosuppression. It is time for a refresher. This review focuses on the key features for each virus that a general physician should be familiar with.

Hepatitis A
Hepatovirus A is a non-enveloped picornavirus, containing a single-stranded RNA packaged in a protein shell. There is only one serotype of the virus, but multiple genotypes exist. Infection with hepatitis A virus (HAV) causes acute viral hepatitis, although rarely leads to chronic hepatitis.1 The prevalence of HAV varies greatly throughout the world with high prevalence in developing countries and low in developed countries. Hepatitis A infection usually results from exposure to contaminated food or water. Infection may be transmitted horizontally, from person to person, although occasionally community outbreaks are reported. A recent hepatitis A outbreak in Australia was reported in 18 patients due to exposure to contaminated frozen berries. These products were successfully recalled and no deaths were reported.2

Due to improvements in both hygiene and sanitation over the last decade, most countries are moving towards a lower prevalence of hepatitis A. In Australia, there are approximately 300–500 cases of hepatitis A reported every year. These cases occur mostly in returned travelers, who have not been vaccinated.3

Vaccination or previous exposure to hepatitis A gives long-term immunity. Post-exposure prophylaxis with immunoglobulin may be indicated when exposure was less than 14 days prior. Vaccine may also be effective. The time from exposure to clinical manifestations is approximately 30 days (range 15–50). Symptoms may be non-specific and include jaundice, anorexia, nausea,
vomiting, abdominal pain and mild fever. Diagnosis is confirmed by identifying anti-HAV immunoglobulin class M (IgM) antibody, detectable 2 weeks after exposure and persisting for up to 14 weeks. The presence of IgG antibodies confirms lifelong immunity from the virus. Jaundice recovers after an average of 6 weeks (range 1–10 weeks).4,5

Rarely, acute liver failure (characterised by jaundice, hepatic encephalopathy and coagulopathy) can result from acute hepatitis A infection. Patients with unrelated liver disease are at increased risk of developing acute liver failure from HAV and as such vaccination should be considered in these patients.7 A relapsing form of acute hepatitis with subsequent peaks of aminotransferase elevation is described in about 10% of patients with hepatitis A.7 A cholestatic form of hepatitis A with prolonged pruritus is also described.

Hepatitis B

Hepatitis B virus (HBV) infection is highly prevalent and responsible for significant rates of morbidity and mortality from liver cancer and liver cirrhosis, in untreated chronically infected individuals. There are estimated 240 million people infected worldwide. The prevalence of chronic hepatitis B (CHB) in Australia is estimated to have increased by more than 50 000 people in the past decade, affecting approximately 1% of the population. This is largely the result of infection in those migrating from high-prevalence countries. Most chronic infection is attributable to mother to child transmission in the absence of accessible infant vaccination programmes.

Screening strategies

Studies in Australia and the United States demonstrate between 30 and 65% of chronically infected adults are unaware they are infected until they were screened. Thus, it is paramount that healthcare providers routinely screen for infection in at risk groups. Screening should include those from hepatitis B endemic countries, renal dialysis patients, patients in correctional facilities, patients who have had household contact or sexual contact and those with other blood-borne viruses. Screening in pregnancy is mandatory to allow appropriate immune prophylaxis and consideration of anti-partum antiviral therapy for the mother, to interrupt the high risk of mother to child transmission (see Pregnancy section below for further information). Patients undergoing chemotherapy or other immunosuppressive treatment are at significant risk of reactivation with serious consequences. These patients should be screened.4–8 Screening is by testing for hepatitis B surface antigen (HBsAg). Further serological testing will distinguish newly acquired or chronic infection (see Table 1). Virology (HBV DNA) and general laboratory (liver function tests (LFT), full blood count (FBC), coagulation) testing allows further characterisation of the phase and consequences of chronic infection.

Phase of infection: immune–virus interactions

The HBV itself is not directly hepatotoxic, despite high viral levels in liver and blood. The clinical outcome is determined by the immunological response. The immune response is minimal in exposed infants after birth with correspondingly few symptoms and minimal biochemical hepatitis. Clearance of infection is rare and chronic hepatitis develops in greater than 90% of those infected at this time. In contrast, exposure to infection, later in life results in symptoms and biochemical hepatitis due to an effective immune response. Clearance usually occurs and chronic infection develops in less than 5% of cases.5,6

Chronic hepatitis B

CHB (HBsAg > 6 months) is a lifelong infection. At any time point, the phase of infection should be characterised, as well as the degree of accumulated liver injury. The five phases of HBV infection are defined according to (although somewhat controversial) pathogenic mechanisms. Patients and clinicians find this terminology hard to understand and remember. In our large volume clinic, we have developed simpler, patient friendly terminology (Table 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Interpreting hepatitis B serology</th>
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<tbody>
<tr>
<td>HBsAg</td>
<td>Anti-HBc</td>
</tr>
<tr>
<td>Acute hepatitis B</td>
<td>Positive</td>
</tr>
<tr>
<td>Chronic hepatitis B (≥6 months)</td>
<td>Positive</td>
</tr>
<tr>
<td>Resolved hepatitis B†</td>
<td>Negative</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>Negative</td>
</tr>
<tr>
<td>Susceptible</td>
<td>Negative</td>
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†May be at risk of reactivation after intense immunosuppression.

Treatment

There are currently two classes of drugs approved for the treatment of HBV infection: (i) direct antiviral agents, nucleos(t)ide analogues (NA), entecavir and tenofovir disoproxil fumarate (TDF); and (ii) pegylated interferon (PEG-IFN). PEG-IFN acts as an immunomodulator, with some weak direct antiviral activity. PEG-IFN has significant side effects, including flu-like symptoms, headache,
fatigue, poor appetite, exacerbation of depression and other psychiatric disorders. Furthermore, it does not have a clear therapeutic advantage, so it remains a less popular alternative. Some evidence suggests that HBsAg seroconversion is more likely with PEG-IFN therapy, when compared with NA although a paucity of controlled trials, using matched populations convincingly demonstrate this. Combination PEG-IFN and NA therapy has recently been shown in a controlled trial to increase the chance of HBsAg clearance from 2.8 to 9%, although these data are encouraging, it is a small difference, not reproduced in other similar studies, and has yet to influence clinical practice greatly.

The safety and durable potency of long-term NA therapy is well described, without appreciable emergence of viral resistance. Monitoring for toxicity is required, as nephrotoxicity and osteoporosis, although uncommon, may occur. A recent, real-world study using 53 500 subjects showed that NA do not increase the risk of renal and bone events, if appropriate toxicity monitoring and dose adjustments are made. A new produg formulation tenofovir alafenamide has been shown to have improved renal and bone safety parameters, resulting from targeted hepatocyte exposure with lower systemic drug levels. The long-term clinical relevance and cost effectiveness of this improved safety profile has yet to be proven.

While NA effectively suppress hepatitis B replication and reduce the risk of disease progression, they cannot clear the replication template of covalently closed circular DNA. HBsAg seroconversion rarely occurs. As a result, most patients require indefinite treatment. The reservoir of DNA template that remains in the liver cell nucleus including covalently closed circular DNA and integrated DNA is not impacted by current therapies. There are several potential therapies for hepatitis B, based on the greater understanding of the hepatitis B life cycle. These therapies aim to achieve a more durable off therapy control or even cure. A target of the sodium/taurocholate co-transporting polypeptide receptor, which inhibits viral entry, Myrcludex B, is an example of such research entering clinical trial phase with some promising very early results.

Decisions to commence therapy are based on the phase of infection, estimated accumulated liver injury and the risk of liver cancer. The primary goal of treatment is to improve patient survival by preventing or delaying the development of cirrhosis and HCC. Secondary goals include (i) HBV DNA suppression, (ii) biochemical and histological improvement and (iii) immunological control of the virus, particularly HBsAg loss and HBsAb development, although rarely achieved. Thus, guidelines recommend that treatment should not be terminated until there is durable HBeAg seroconversion with minimum of
6 months consolidation or in patients who are HBeAG negative, HBsAg clearance6–10 (Table 3).

Initiation of therapy in the damage (immune clearance) and escape (immune escape) phase to prevent injury or in patients with established liver cirrhosis to reverse injury is recommended. Treatment is not usually indicated in young patients during the silent (immune tolerant) phase, although viral levels are high, liver injury is not occurring. In addition to clinical parameters, patient’s wishes, anticipated compliance and consideration of any contraindications to treatment are considered prior to commencing treatment.

**Special groups**

**Hepatitis B infection and immunosuppressive therapy**

As the immune system response to hepatitis B is critical for its control, it is not surprising that immunosuppressive therapy such as chemotherapy, biologic therapy or corticosteroids (high dose or greater than 4 weeks duration) result in increased viral replication. Subsequent immune reconstitution, occurring usually after the completion of chemotherapy may precipitate a powerful response to virus and severe liver injury. The risk of reactivation in HBsAg-positive patients undergoing chemotherapy is between 33 and 60%.20 Reactivation can lead to liver failure, death or interrupt cancer treatment, increasing morbidity and mortality. Mortality (primarily related to liver failure) is between 5 and 50%. High baseline serum HBV DNA or high alanine aminotransferase (ALT) prior to commencing immunosuppressive therapy increases risk.6–21 Universal HBsAg screening is critical prior to initiation of immunosuppressive therapy. Multiple studies have shown that pre-emptive antiviral therapy with NA will prevent complications and is proven superior to a response at the time reactivation occurs.22 Antiviral therapy should be continued for between 6 and 12 months after completion of immunosuppressive therapy. Stopping antiviral therapy may not always be appropriate, such as when there is significant liver injury at baseline, a viral load > 2000 IU/mL or if repeated courses of immunosuppressive therapy are required.5,8,10

Intense immunosuppression, such as with haemopoietic stem cell transplantation, or B-cell ablation with agents such as rituximab, can result in reactivation of resolved HBV infection (anti-HBcAb positive). While less likely, overall this large at risk population will get into trouble if ignored, as fulminant hepatitis and hepatitis-related mortality can occur. For example, HBV reactivation occurred in 17 out of 150 lymphoma patients with resolved HBV infection treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone).20 Despite this evidence, universal HBV screening and initiation of treatment prior to immunosuppressive therapy is not routinely practised by all oncologists. A survey in 2011 showed that only 19% of oncologists practised universal screening.23 Guidelines recently reported by American Gastroenterological Association for most settings of immunosuppression report risk of reactivation with each HBV and immunosuppressive scenario. Where the risk is low (1%), such as in those with resolved HBV infection and treatment with biologic anti-biologic modifier therapies, the choice between monitoring and pre-emptive therapy is based on cost and patient preference.24

**Pregnancy**

Mother to child (perinatal) transmission through exposure to blood or blood contaminated fluids at or around, the time of birth25 is the most common mechanism for transmission of HBV worldwide. In Australia perinatal transmission despite immune-prophylaxis occurs in HBeAg-positive mothers (7%) and from mothers with high viral loads (HBV DNA ≥ 7 log10 IU/mL) approaching 10%.26 The mode of delivery or breastfeeding is not relevant. Antepartum antiviral therapy when HBV DNA ≥6.5–7 log10 IU/mL (to allow room for minor laboratory

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**Table 3** End point of hepatitis B therapy with nucleos(t)ide analogues

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<thead>
<tr>
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<tbody>
<tr>
<td>HBeAg positive</td>
<td>Until HBeAg seroconversion followed by 12 months of consolidation</td>
<td>Until HBeAg seroconversion followed by 12 months of consolidation + undetectable DNA</td>
<td>Until HBeAg seroconversion followed by 12 months of consolidation + undetectable DNA</td>
</tr>
<tr>
<td>HBeAg negative</td>
<td>HBsAg clearance</td>
<td>HBsAg clearance†</td>
<td>Treatment for at least 2 years + DNA undetectable three times 6 months apart</td>
</tr>
</tbody>
</table>

†Insufficient evidence to support stopping HBV therapy in this group of patients. Persons who stop antiviral therapy should be monitored every 3 months for at least 1 year for recurrent viraemia, ALT flares and clinical decompensation.
variation) commencing at 32 weeks of gestation reduces the risk of perinatal transmission effectively.\textsuperscript{22,26} Tenofovir is safe and well tolerated, by mother and baby, with no increase in detectable congenital malformations or negative obstetric outcomes reported.\textsuperscript{22,26} The threshold at which to introduce TDF has been a topic of some controversy in the literature, and some guidelines suggesting a lower threshold, such as 5 \( \log_{10} \) IU/mL while acknowledging the data to support this is limited.\textsuperscript{6,28} Risks and benefits of antiviral therapy should be discussed with mothers with a high viral load, prior to the third trimester.

The optimum management post-partum is uncertain. High rates of post-partum flares are reported.\textsuperscript{30} Extended therapy post-partum beyond the indication of preventing mother to child transmission is not of proven benefit. At the present time, continuation to between 4 and 12 weeks post-partum is reasonable, unless another indication such as significant liver disease is present. The majority of post partum flares settle spontaneously within 6 months and extended therapy is not usually required in a large reported Australian cohort.\textsuperscript{28}

### Hepatitis C

Chronic hepatitis C virus (HCV) infection affects approximately 230,000 Australians, who are at risk of progressive liver fibrosis leading to cirrhosis, liver failure and HCC. HCV infection is now curable, and viral eradication is associated with multiple clinical benefits, including improvement in quality of life, loss of infectivity, regression of cirrhosis, reduction of mortality, lower risk of liver failure and HCC. Until recently, the treatment of HCV involved interferon therapy, which had limited efficacy and was poorly tolerated. Since March 2016, DAA therapies have become available for any Australian with HCV. DAAs are highly effective and well tolerated.\textsuperscript{31,32}

### Screening and diagnosis

Infection with hepatitis C is usually associated with identifiable risk factors, particularly history of intravenous drug use, non-sterile tattooing, blood transfusion before 1987 and immigrants from developing countries who may have been exposed to HCV during non-sterile procedures. In addition to screening at risk populations, the Centre for Disease Control and Prevention recommends universal screening in those born between 1945 and 1965.\textsuperscript{33} This acknowledges that risk factors may not always be evident. HCV antibody is recommended for HCV screening, indicating current or past exposure. Current HCV infection is confirmed by a polymerase chain reaction assay for HCV RNA. A minority (25%) of acute HCV infections will clear spontaneously within 6 months. There are seven different HCV genotypes (genotypes 1–7). The common genotypes in Australia are genotypes 1 and 3. HCV genotyping is necessary prior to treatment initiation as approved regimens are genotype-specific.\textsuperscript{12}

### Evaluating for the presence of cirrhosis

Identification of cirrhosis is important prior to treatment for two reasons: (i) treatment duration for some genotypes need be longer to achieve cure and (ii) those with cirrhosis continue to have a risk of hepatocellular cancer following successful eradication of the HCV, thus surveillance with regular ultrasounds is required.\textsuperscript{34} Liver biopsy was once the gold standard for the diagnoses of cirrhosis now rarely performed due to pain, risk of serious adverse consequences and non-invasive alternatives.\textsuperscript{35} Transient elastography, or Fibroscan is a well-validated non-invasive tool to measure liver stiffness. Fibroscan is available in most metropolitan centres. A liver stiffness above 12.5 Kpa is a reliable threshold for identifying cirrhosis. The Fibroscan result, coupled with clinical examination, biochemical and radiological information are used synergistically to identify those with advanced fibrosis and cirrhosis. A reliable reading may be unachievable in 10% of patients, particularly those who are obese or with ascites.\textsuperscript{36} Reasonably accurate identification of cirrhosis is also possible with formulas incorporating serum biomarkers, such as the validated APRI score (aspartate aminotransferase (AST) to platelet ratio index). A systematic review including 172 studies conducted in patients with hepatitis C reported a median Area under Receiver Operator Characteristic (AUROC) of 0.77 and 0.84 for the APRI score, when used to identify patients with cirrhosis.\textsuperscript{37}

### Treatment

All patients with HCV (genotypes 1–4) should be considered for short-term (8–24 weeks) Pharmaceutical Benefits Scheme (PBS)-funded interferon-free DAA therapy. DAA agents target multiple steps in the HCV replication life cycle (Table 4). DAAs are highly effective and safe; they are used in combination to avoid resistance. The goal is cure proven by undetectable plasma HCV RNA at least 12 weeks after treatment is completed (sustained virological response). Previous treatment experience, presence of cirrhosis, genotype and renal failure (EGFR <30) all influence the choice and duration of treatment (Table 5). Zepatier (elbasvir/grazoprevir) is the most recently approved interferon-free regimen, also effective for genotype 1 but extending opportunity for those with genotype 4, and those with EGFR <30. PBS supported...
treatment for the uncommon genotypes continues to support PEG-IFN-alpha and ribavirin, although alternative pan-genomic DAA combination therapies are likely to be funded in the next few years. Gastroenterology Society of Australia Guidelines for the assessment and treatment of hepatitis C in the era of DAA therapy include recommended regimens and guide for assessment and monitoring (Table 5).

When prescribing hepatitis C therapy, potential drug interactions should be determined as some may cause adverse reactions, or altered efficacy of the medication or the DAA therapy. Internet-based resources such as University of Liverpool HEP drug interactions (http://www.hep-druginteractions.org) are useful. Assessing and managing anything that may affect adherence is also critical (see Table 6: Checklist prior to commencing DAA therapy for hepatitis C). Primary care doctors may prescribe DAA therapy, after consulting a gastroenterologist or infectious diseases physician or if they have sufficient experience in hepatitis C treatment (PBS requirement). Monitoring after initiation of therapy with a DAA in a non-cirrhotic generally involves a blood test at week 4 of most DAA therapy (EUC, LFT and FBC) or week 8 if the patient is taking Zapatier (elbasvir/grazoprevir). Testing (HCV RNA, EUC, LFT, INR and FBC) 12 weeks after completing treatment to confirm complete eradication of the virus or sustained viral response is also important as some, although only a few, will fail and need a second-line therapy.

Hepatologists and infectious diseases specialists will not have capacity to eradicate hepatitis C without help from community general practitioners, drug health and sexual health doctors. Novel telementoring programmes, such as Project ECHO (Extension for Community Healthcare Outcomes) has been demonstrated to expand expertise in hepatitis C treatment (PBS requirement). Monitoring after initiation of therapy with a DAA in a non-cirrhotic generally involves a blood test at week 4 of most DAA therapy (EUC, LFT and FBC) or week 8 if the patient is taking Zapatier (elbasvir/grazoprevir). Testing (HCV RNA, EUC, LFT, INR and FBC) 12 weeks after completing treatment to confirm complete eradication of the virus or sustained viral response is also important as some, although only a few, will fail and need a second-line therapy.

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Direct-acting anti-viral</th>
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<tbody>
<tr>
<td>NS3 protease inhibitor</td>
<td>Paritaprevir Grazoprevir</td>
</tr>
<tr>
<td>NS5B nucleotide inhibitor</td>
<td>Sofosbuvir</td>
</tr>
<tr>
<td>NS5B non-nucleotide inhibitor</td>
<td>Dasabuvir</td>
</tr>
<tr>
<td>NSSA inhibitor</td>
<td>Ledipasvir Ombitasvir Daclastavir Elbasvir</td>
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The viral hepatitis alphabet

HCC is one of the leading causes of cancer deaths worldwide, with nearly 700 000 deaths attributed to HCC each year. Liver cancer is the fifth most common cancer in men and the eighth in women. While the burden of HCC is highest in Asia and Africa, its incidence is rising in the developed world, in countries such as the United Kingdom, France, the United States and Australia. The majority of HCC in both developed and developing countries is attributable to CHB and hepatitis C, although non-alcoholic steatohepatitis is an emerging significant aetiological factor and co-factor. Cirrhosis is present in 80–90% of patients with HCC, in the remainder hepatitis B is regarded as a direct carcinogen. The 5-year cumulative risk for the development of HCC in patients with cirrhosis ranges between 5 and 30%, depending on the underlying aetiology (more common in HCV), region or ethnic group (more common in people from Asia) and stage of cirrhosis (highest risk in patients with decompensated disease).

The risk of HCC in CHB infection is increased in patients who are male, elderly, have long duration of infection and have a family history of HCC. National hepatitis B vaccination programmes have dramatically reduced the prevalence of hepatitis B infection, and the incidence of HCC. Since the inception of a universal vaccination programme in Taiwan, the incidence of HCC in children between 6 and 14 years of age has fallen by 65–75%.

Screening utilising 6 monthly imaging by ultrasound has been recommended by the American Association of the Study of Liver Diseases (AASLD) (Table 7). Testing for alpha-fetoprotein (AFP) tumour marker at the same time is not recommended because of issues with false-positive results in the setting of liver inflammation. In practice, AFP in conjunction with a liver ultrasound is still used in many hepatology practices. Surveillance for HCC is often underutilised in patients with cirrhosis. In a study of 1873 patients diagnosed with HCC above the age of 65, in whom cirrhosis was recorded for 3 or more years, only 29% had received routine surveillance and a further 33% received inconsistent surveillance. Despite limited data from randomised clinical trials, early detection offers the best chance for curative treatment for patients with HCC, increasing the possibility for early curative treatment.
Hepatitis delta

Hepatitis D (delta) virus (HDV) is a small, defective RNA virus that requires HBsAg for transmission and packaging. HDV is considered to be a sub-viral satellite because it can propagate only in the presence of the HBV. The HDV genome consists of a single-stranded RNA, which is folded as a rod-like structure through internal base-pairing. Transmission of HDV can occur either via simultaneous infection with HBV (co-infection) or superimposed on CHB or hepatitis B carrier state (super-infection).

Of the 350 million individuals with chronic HBV infection, approximately 15 million have also been exposed to HDV. While HDV is relatively common in the Mediterranean basin, HDV is not common in Australia. It is estimated that there are approximately 30 cases reported per year. Acquiring HBV and HDV during the same exposure (coinfection) is associated with more severe acute hepatitis and higher mortality, when compared with acute HBV mono-infection. HDV super-infection in an HBV carrier can manifest as an acute hepatitis although usually results in chronic HDV infection. The progression to cirrhosis is faster in patients with chronic HDV, when compared with HBV mono-infection: 80% of patients with chronic HDV will progress to cirrhosis in 5–10 years.

The fate of HDV is determined by the host response to HBV, and HDV is cleared if HBV is cleared. HBV DNA is cleared if HBV is cleared. HBV DNA is cleared if HBV is cleared. HBV DNA is cleared if HBV is cleared.
usually low or negative in chronic HDV infection, because HDV suppresses HBV replication. HDV IgM is positive in acute infection and can persist in chronic infection; if it does persist, it can be used as a surrogate marker for HDV replication. Qualitative HDV RNA is a marker of viral replication that is positive in chronic infection. HDV RNA is useful to monitor treatment response, but is not readily available. Furthermore, HBsAg is useful to monitor treatment response if quantitative HDV RNA is not available.54

The mainstay of treatment for HDV infection is PEG-IFN-alpha for at least 48 weeks. Efficacy is disappointing, with control of infection estimated in only 20–25% of the patients, worse in those with cirrhosis.55,56 The oral nucleos(t)ides appear to have limited activity against HDV, because the virus uses host enzymes for replication and thus lacks enzyme targets.56 Nevertheless, control of HBV is always indicated and after long-term therapy, delta viral levels can decline. New targets, such as with Myrcludex B a first in class entry inhibitor inactivating the HBV and HDV receptor are promising but results are preliminary.57 Patients with HDV should be managed in a specialist centre.

**Hepatitis E**

Hepatitis E is one of the most frequent causes of acute hepatitis worldwide. An estimated 70 000 deaths are attributed hepatitis E virus (HEV) genotypes 1 and 2 every year. The majority of infections are thought to remain asymptomatic.58 HEV is a small, non-enveloped virus with a single-stranded RNA genome. The virus has four genotypes. Genotypes 1 and 2 exclusively infect humans, whereas genotypes 3 and 4 infect humans, pigs and several other mammalian species. HEV is endemic in many countries of Asia, Africa, Middle East and Central America. The transmission of HEV is faecal-oral, usually through contaminated drinking water.59 HEV is not a common cause of liver disease in Australia. The first case of HEV was reported in 1993.2 Over the last 6 years, there have been approximately 30–40 cases of hepatitis E diagnosed every year, predominantly in returned travellers. However, a recent cluster of HEV infection linked to a single restaurant in Sydney in May 2014 was the first reported Australian outbreak of locally acquired HEV infection, and one of the largest linked with a restaurant reported anywhere. A total of seventeen cases were linked to consuming pork liver pâté at this restaurant during a 9-month period.60

Clinically, acute HEV infection is similar to hepatitis A; however, a longer incubation period, a longer clinical course, a higher fatality among pregnant women, patients with pre-existing liver disease and patients with HIV and dialysis patients is also described. The clinical course of acute HEV infection is characterised by a 3–8-week incubation period, during which HEV RNA can be detected in the stool or serum. After 8 weeks, symptoms develop in some patients and are usually accompanied by a rise in ALT and the appearance of anti-HEV IgM. IgM persists for months and declines with the resolution of infection.56 Suspected HEV infection in immunocompromised patients should also be confirmed by HEV RNA testing. Chronic hepatitis does not usually develop after acute HEV infection, except in the transplant setting and possibly in other settings of immunosuppression. Patients with chronic hepatitis E infection may develop liver cirrhosis.61 Ribavirin has become the drug of choice for chronic HEV and its efficacy has been proven in larger studies.62 As hepatitis E is normally self-limiting, most patients do not require specific treatment, other than supportive care.

Two candidate vaccines against hepatitis E have undergone successful clinical testing. The first (56-kDa truncated ORF2 protein of HEV) achieved 100% seroconversion and protective efficacy of up to 95.5% during a 2-year follow up of 2000 patients.63 The second vaccine (ORF2 protein) showed a protective efficacy of 100% during a 13-month follow up. The use of this vaccine was approved in China in 2012.64 Unfortunately, this vaccine has not been licenced for marketing in other countries, due to lack of profitability. Currently, the best way to prevent hepatitis E is by the provision of safe drinking water, proper disposal of human faeces and education about personal hygiene.

**Conclusion**

The aim of this review was to provide a clear and up-to-date synopsis of hepatitis A to E. Understanding pathogenesis, assessment of their impact and therapeutics is crucial. This field has evolved considerably in the last few years and will continue to do so. There are multiple resources including the Gastroenterological Society of Australia65 and the American Gastroenterological Association,66 which can assist physicians with more detailed information, when assessing and treating patients with viral hepatitis.
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Advance Care Planning: is quality end of life care really that simple?

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Key words
advance care planning, terminal care, end of life, advance directives, bioethics.

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Abstract
The routine implementation of Advance Care Planning (ACP) is now a prominent feature of policy directed at improving end of life care in Australia. However, while complex ACP interventions may modestly reduce medical care at the end of life and enable more people to die at home or outside of acute hospital settings, existing legal, organisational, cultural and conceptual barriers limit the implementation and utility of ACP. We suggest that meaningful improvements in end of life care will not result from the institutionalisation of ACP but from more significant changes to the design and delivery of care.

Introduction
Over the past three decades a large, international body of work has been conducted with the goal of improving the quality of end of life care (EOLC). Some of the most extensive work has been directed at improving decision-making and care at the end of life (EOL) through institutionalisation of Advance Care Planning (ACP). In 2015, the National Palliative Care Programme, in Australia, funded a number of programmes, including: Austin Health to continue Respecting Patient Choices; Palliative Care and Advance Care Planning in General Practice – A training package for Practice Nurses; and the Decision Assist project which provides specialist palliative care and ACP advisory services nationally to aged care providers and general practitioners. National and state-based policy has also been widely implemented mandating the routine uptake of ACP.1–3 including the National Palliative Care Strategy, which supports ‘the national roll out of ACP across all sectors’.3 This focus on ACP is in line with international experience, demonstrated by ‘a nearly two-fold number of publications on the topic in 2010–2015 compared to 2005–2010, an increased number of ACP interventions and guidelines incorporating ACP, and increased media attention to the topic’.4

The conceptual justification for ACP is grounded in the principle of patient autonomy – the notion that clarifying and respecting the wishes of patients regarding their EOLC may extend their autonomy into states of future incapacity. However, despite professional and political support for ACP, there is limited empirical evidence to support its use.4–6 In this paper, we contend that ACP is implemented not only as a solution for an ethical problem (to do with patient autonomy),6 but also as a solution to an applied problem, that is, as a means of encouraging and systematising quality improvements in EOLC. We argue that not only are these two objectives vastly different but that ACP has a limited capacity to meet either of these objectives. Further, we suggest that in the rush to implement ACP, research has failed to consider adequately the gap between patient autonomy and quality care, or to consider the constraints of structural problems, such as low uptake and implementation barriers in using ACP as a solution to systematising quality improvements in EOLC.

The gap between patient autonomy and quality care
Irrespective of how ACP interventions are designed or implemented, they are all based on the assumption that respecting and extending autonomy is central to achieving a ‘good death’. A critical analysis of EOL research
suggestions, however, that the central importance of autonomy in achieving a good death is not self-evident.

While several studies reveal that many patients with advanced disease prefer to maintain their autonomy and to be engaged actively in medical decision-making, not all patients are willing and able to do so. A review of perceptions and experiences of ACP in cancer care (by author and colleagues) reported that some patients strongly rejected ACP, preferring not to discuss what may happen in the future. Likewise, Bollig et al. reported that Norwegian nursing home residents may not consider ACP to be important. More significantly, even for those who wish to engage in ACP, the true value of ACP to patients may have little to do with control over decision-making in times of incapacity and more to do with the quality of care received. While numerous studies describe how chronically ill patients identify ‘achieving a sense of control’ as important to quality EOLC, this is often not framed in terms of control over individual decisions but instead in terms of being respected, listened to and consistently having psychosocial concerns addressed. A US survey of patients and practitioners regarding factors considered important at the end of life provides evidence to support this. While approximately 50% of patients agreed that controlling the time and place of death was important, almost all respondents valued attributes associated with ‘being treated as a whole person’. Likewise, another review of the elements of EOLC that patients ranked as being important showed that quality EOLC is not simply a matter of preference expression or control over decision-making, but a complex amalgamation of: effective communication; shared decision-making; expert care; respect and compassion; trust and confidence in clinicians; an adequate environment for care; and strategies that minimise the burden on families.

These studies suggest that not all patients desire control over their treatment choices and that while many patients value their autonomy in regards to treatment choices, they may prioritise other aspects of EOLC. If the insights provided by these studies are correct, they suggest that EOLC should focus less on the authorisation of patients’ previously expressed treatment preferences and more on building relationships, shared decision-making and service provision.

**ACP as a way of encouraging and systematising quality care**

We contend that ACP has both a philosophical purpose (advancing autonomy) and an applied purpose (systematising quality care). In other words, the function of ACP is not only to support patient autonomy but also to enable the healthcare system to reduce intensive treatment at the EOL, reduce costs of care, support bereaved families and standardise practice. If one accepts that this is true, that ACP has a dual purpose, then in order to meet its applied or institutional purpose, ACP must be successfully, systematically and sustainably implemented.

It is important to note that there are significant barriers to the successful implementation of ACP. First, providing care to people who are dying requires sensitivity, integrity, commitment, time, compassion and skills in clinical practice and in communication. These skills and virtues cannot be assumed and arguably require training to ensure health professionals understand and are competent in decision-making and EOLC. Second, successful ACP requires consistency in the systematic transfer of information between healthcare providers. This is particularly challenging because many ACP discussions occur in the community and/or outpatient setting between patients and primary care or specialist physicians – practitioners who may ultimately not be involved in the inpatient or EOLC of the patient. Hospital-based and emergency care staff also commonly do not have access to outpatient records that document ACP discussions. While electronic prompts encouraging patient engagement in ACP, and modifications of the electronic record to document patients’ wishes may assist ACP, these are not routinely implemented and in themselves are not a solution. Third, the systematic implementation of ACP requires significant financial investment in health service delivery. Swerissen and Duckett, for example, have estimated that increasing community-based support for people who choose to die at home in Australia would cost $84 million even accounting for savings due to reduced aggressive medical intervention at the EOL. Lastly and perhaps most importantly, while it is increasingly expected that ACP become a part of standard practice, there has been no sustained resourcing or workplace reforms to change meaningfully professional practice or to create the time required to do ACP well. While United States physicians are now re-imbursed under Medicare for 30 min of their time to have ACP discussions, similar initiatives are not standard practice in Australia. Given the time required to do ACP well it is arguable that initiatives such as these are required to begin to address both the logistical and financial barriers to successful implementation.

With this in mind it is unsurprising that international data suggest the frequency of EOL discussions remains low. As others have noted, doing more of the things that facilitate delivery of ACP (such as the creation of specialist facilitators and implementation of policy) will not reduce the effects of those things that undermine or
create barriers to it. Lund et al. contend that interventions most likely to meet with success are those that make elements of ACP workable within complex and time pressured clinical workflows. We agree with Lund and contend that the routine implementation of ACP will only occur where more time is created for doctors to have ACP and EOL discussions with patients and their carers (which would require changes to how they are funded and to how their time is allocated), more support is provided for increasing community healthcare services to relieve the burden on hospital systems, and more attention is given to improving medical records and optimising care coordination between community, specialist outpatient and hospital-based services.

The empirical evidence for ACP

Complex ACP interventions, which refocus attention away from particular documents to a broader, ongoing process of communication appear to have some beneficial effects on care. Ten reviews of the empirical evidence regarding the efficacy of ACP have been published; one meta-analysis, six systematic reviews, one narrative review, one Cochrane systematic review (no results) and two Health Technology Assessment. Three of these reviews reported positive effects. Namely, that more complex ACP interventions may increase the frequency of out-of-hospital care (decreased hospitalisations and increased hospice use) (three of five studies) and out-of-intensive care unit care (one of three studies) and increase compliance with patients’ end-of-life wishes (three of four studies). However, none of these reviews found that ACP had a significant impact on symptom management, symptoms in the last week of life, caregiver strain, patient anxiety, patient depression and several aspects of patients’ physical and social functioning. Seven reviews found no evidence, limited evidence, or equivocal evidence to support the efficacy of ACP.

ACP may have a role to play in improving EOLC, by allowing more people to receive care outside of hospital and increasing compliance with patients’ end-of-life wishes. However, despite rhetoric in support of ACP few studies have provided any evidence demonstrating the effectiveness of ACP, with most studies reporting no beneficial effect or equivocal results. Furthermore, what evidence there is is generally of low quality. For example, Houben et al. reported that 55.4% of the trials included in their review were classified as ‘low-quality trials’, commenting that this ‘may have influenced the findings of the included trials’ and they may include ‘biases, like overestimation of clinical effectiveness’. Additionally, not all of the positive effects reported align with ACP stated purpose. ACP programmes are most commonly evaluated in terms of ‘process’ and a large number of measures address the issue of use of care – focusing on avoiding certain treatments, rather than enhancement of patient preference or patient experience. Notably, there is no convincing evidence to demonstrate the effectiveness of ACP on patient-centred outcomes, such as psychological well-being. There is a lack of research into patient experience, different ethnic groups and community settings. Last, evidence regarding ACP must be reviewed in light of the real world context. In this regard, the fact that ACP has generally failed to be systematically and successfully implemented raises serious questions regarding whether ACP interventions can meaningfully or significantly enhance patient autonomy or improve EOLC outside of the optimised setting of clinical trials.

Refocusing the debate around EOLC and reducing attention to ACP

Whilst it is undeniable that patients should be respected and receive care consistent with their goals, values and treatment preferences, ACP is mired in conceptual ambiguity. The stated purpose is variable (enhancing autonomy, reducing intensive treatment at the EOL, decreasing family distress) and inconsistently applied. Furthermore, issues persist regarding the implementation and efficacy of ACP. It is critical that these limitations are addressed because the modest benefits of ACP are unlikely to be realised unless we recognise that quality EOLC requires more than simply the autonomous expression of preferences for care; and that ACP is complex, difficult, time consuming and requires adequate resourcing and training to enable staff to develop the expertise and devote the time required to enact ACP properly.

It is critically important that we clearly acknowledge the limitations of ACP. First, because widely held assumptions that ACP is an ‘un-equivocal good’ acts as a heuristic – directing our thinking and policy making in ways that are ultimately unlikely to meet the needs of dying patients. This also acts to divert attention from other important domains and policies required to improve EOLC. Second, perpetuating unrealistic assumptions regarding the efficacy and benefits of ACP may prevent us from asking whether the opportunity costs of ACP are unacceptable. Specifically, whether the investment and re-structuring required to enact the meaningful implementation of ACP is ‘worth’ the modest and variable impact it has on EOLC.

Given this, it is appropriate that we ask whether continued political and professional focus on ACP is
Conclusions and practice implications

Improving EOLC is not an easy task, particularly as care becomes increasingly fractured, technology driven and complex. It is unlikely that any single mechanism, particularly one that emphasises decision-making, will achieve sufficient quality care. This suggests that we should look beyond ACP to the broader political and moral foundations of care.

References


Supporting Information

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

Appendix S1. Methods and summary of results for literature search of empirical evidence in ACP.

MEDICAL EDUCATION

The clinical academic workforce in Australia and New Zealand: report on the second binational summit to implement a sustainable training pathway

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Abstract

There has been a decline in the proportion of clinical academics compared with full-time clinicians, since 2004. A Working Party was established to help develop and implement a model for the training of clinical academics. After a highly successful first summit in 2014 that summarised the challenges faced by clinical academics in Australia and New Zealand, a second summit was convened late in 2015 to report on progress and to identify key areas for further action. The second summit provided survey results that identified the varied training pathways currently offered to clinical academics and the institutions willing to be involved in developing improved pathways. A literature review also described the contributions that clinical academics make to the health sector and the challenges faced by this workforce sector. Current training pathways created for clinical academics by Australasian institutions were presented as examples of what can be done. The perspectives of government and research organisations presented at the summit helped define how key stakeholders can contribute. Following the summit, there was a strong commitment to continue to work towards developing a sustainable and defined training pathway for clinical academics. The need for a coordinated and integrated approach was highlighted. Some key objectives were agreed upon for the next phase, including identifying and engaging key advocates within government and leading institutions; publishing and profiling the contributions of successful clinical academics to healthcare outcomes; defining the stages of a clinical academic training pathway; and establishing a mentoring programme for training clinical academics.

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Introduction

Clinical academics are clinician leaders who, through training and experience, have decided to make research and/or education a significant part of their professional career, and are fundamental to this process. The proportion of clinical academics in the workforce has been steadily declining over recent decades. This has the potential to have a serious impact on medical education, research and health outcomes. The current training of clinical academics is largely ad hoc. Two Australasian summits, held in 2014 to understand the challenges faced by clinical academics in the current environment and 2015 to identify the stages of current training pathways and to decide on future direction, have highlighted the need to create a sustainable clinical academic workforce by providing defined and supported pathways for each stage of their training. These summits were convened to discuss this challenge and to develop a plan of action. Representatives of organisations providing education, training, research and patient care within the healthcare sector and government representatives from Australia and New Zealand were involved as well as representatives of funding bodies whose support will be required for the implementation of future clinical academic training pathways.

In 2003 there was a movement to reinvigorate academic medicine, led by representatives of the British Medical Journal, and they established the ‘International Campaign to Revitalise Academic Medicine’ (ICRAM). This global initiative consisted of 20 clinical academics from 14 countries. This large geographical spread made it difficult to reach consensus and thus five different scenarios were developed to aid the future development of academic medicine. The present initiative has the potential advantage of focusing on only Australia and New Zealand.

The aim of the first summit was to bring together all stakeholders to identify strategies to support the training of clinical academics in Australia and New Zealand. There was an open invitation to all interested parties, with the summit attracting attendees from a broad range of sectors and disciplines, including government and policy in health, education and research, training and education across the continuum, healthcare provision and management, regulatory and accreditation, industrial and advocacy. The first summit examined the UK Foundation Programme to identify key successes and challenges and how they relate to our systems. Key features of this programme are that it spans medical school through to definitive appointment and that it runs a programme in parallel with clinical training with defined and funded positions at each stage. Following the inaugural summit a Working Party on Clinical Academic Pathways was established with members from the Royal Australasian College of Surgeons (RACS), the Royal Australasian College of Physicians (RACP), Medical Deans Australia and New Zealand, the Australian Academy of Health and Medical Sciences (AAHMS), the Australian Medical Council (AMC) and the Australian Medical Association (AMA). This working party is not exclusive and actively seeks engagement with all interested parties.

The second summit

The second summit took stock of the progress achieved during 2015, reviewed the different training pathways at selected healthcare organisations and formed an action plan with the goal of implementing a sustainable training pathway for clinical academics in Australia and New Zealand. The second summit again attracted key stakeholders and specifically those with experience of different types of training pathways for clinical academics.

The opening address as the second summit was by Professor John Windsor, a member of the Working Party on Clinical Academic Pathways and an RACS representative from New Zealand. He highlighted the vital and disproportionate contribution of clinical academics to the health sector. He explained that the decline in the number of clinical academics and the ad hoc nature of their training were the primary stimuli for these summits. The urgent task of training and reinvigorating the clinical academic workforce were emphasised and that the responsibility for addressing the looming crisis was necessarily a shared one.

The results of the survey and literature review

Professor Julian Smith, Chair of the Working Party on Clinical Academic Pathways and a RACS representative, presented the findings from a survey designed to: (i) understand the perceived importance of clinical academics; (ii) describe current training pathways in Australia and New Zealand; and (iii) identify potential pathways and funding sources that might serve as exemplars for the implementation of a pilot programme. The survey was distributed among healthcare-related organisations in Australia and New Zealand (university medical schools, teaching hospitals, medical research institutes and the learned medical colleges).

The survey response rate was 30% (47/156) with the majority of responses received from University Medical Schools and Teaching Hospitals. An overview of the survey results is shown in Table 1. There was a resounding...
endorsement of the importance of clinical academics by 92% of respondents. However, only 31% (16/47) of responding organisations currently offer a defined training pathway for clinical academics. These included PhD programmes, intercalated degrees during medical school and mentorship programmes. Current pathways include support in varying combinations such as research opportunities, academic mentoring, administrative and technical support, specific courses and a written curriculum. Funding for these pathways comes from internal scholarships/fellowships, direct funding from the organisation, state government funding or the National Health and Medical Research Council (NHMRC). A specific mentoring programme had been offered by 43% (6/14) of responding organisations with established clinical academic pathways.

Responses to questions regarding potential future pathways for clinical academics demonstrated that only 7% (2/27) of the respondent organisations were planning on implementing training pathways in the future, but 22% (6/27) would be willing to fund/support the implementation of future training pathways. These willing organisations will be approached by the Working Party on Clinical Academic Pathways to consider piloting model training pathways. It was noted that within Australia and New Zealand several universities are offering intercalated research degrees, such as a dual MBBS-PhD (now a MD-PhD) from the Universities of Sydney6 and Auckland.7

Dr Tamsin Garrod, a research and administrative support for the Working party, presented a literature review that focussed on the multiple contributions of clinical academics to the health sector. It was noted that the benefits of clinical academics have not been widely studied. This is likely due to the challenges in comparing settings that are research active and support trainee academic clinicians with those that do not.8 It might also reflect the difficulty in measuring the contributions to clinical care, training, research, administration and quality improvement in hospital settings. It is recognised that the contribution of clinical academics is aided by the proximity to patients helping to identify the important research questions, the ability to translate research from bench to bedside and the recruitment of patients for clinical studies.9,10 Clarke et al.11 reported a potential association between hospitals that perform clinical trials and improved patient outcomes, but concluded that further research was required to confirm this.11 A recent systematic review conducted by the Commonwealth Scientific and Industrial Research Organisation (CSIRO) finds a positive correlation between research culture and patient outcomes.12 Additional studies found very little difference in the patient outcomes from teaching and non-teaching hospitals. The review also highlighted the specific challenges faced by the clinical academic workforce, and the importance of clearly defined training posts for sustaining this workforce. In Australia and New Zealand the challenges include the lengthy duration of training, the lack of financial parity with full-time clinical staff and the heavy reliance on relatively limited (c.f. UK and USA) and competitive research funding.13,14

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Current models for training of clinical academics
The second session provided presentations outlining existing clinical academic training pathways in Australia
and New Zealand. These were considered some of the best examples available, and it was hoped that by profiling these would be a stimulus for the development of an intentional and integrated approach to clinical academic training.

Professor Jeffrey Zajac, from Austin Health, Melbourne, highlighted the emphasis placed by the health service on research, and its formal affiliation with a number of research institutes and universities. For Austin Health this means that currently able to support 108 students doing higher degrees in areas including infectious diseases, cardiology and respiratory disease. Austin Health, as a healthcare provider, actively fosters a research culture and encourages career-long learning and teaching. Improvements to the career pathway would include circumventing the sometimes ad hoc training period, and direct more funding to PhD Scholarships and Fellowships at an earlier stage in the career of a clinical academic seeking research training.

Professor Andrew Hill presented the clinical academic pathway offered at the University of Auckland. Informal training pathways have been developed across a number of different medical specialties. It was noted that the remuneration for clinical academics in Auckland was reasonably equivalent to full-time clinicians, which has been important for recruitment and retention. One of the limitations of the clinical academic training pathway has been the major difficulty in obtaining sufficient funding for the necessary number of positions and the variable manner in which these training pathways have been established. A more intentional and formal training pathway would likely produce more growth in the numbers of participants and the quality of research and health outcomes.

Professor Julian Smith described the goals of the Monash Partners Academic Health Science Centre, established in 2011 and now has in excess of 2500 research staff. Participants include Monash Health, Alfred Health, Monash University, Cabrini Health, Epworth HealthCare, Baker IDI Heart and Diabetes Institute, Burnett Institute and Hudson Institute. The Centre specialises in multiple research areas, ranging from cancer and haematological diseases, to neuroscience and mental health. Several Clinician Practitioner Fellowships, which fund part-time research, are awarded each year to post-doctoral clinicians in the early stages of their clinical academic career.

Dr Cate Kelly, Director of Medical Services, outlined the current situation at Alfred Health, which currently employs 1300 medical staff and of whom 63 are senior clinical academics across the Alfred, Sandringham and Caulfield Hospitals. Alfred Health is a founding member of the Monash Partners Academic Health Science Centre, offers a supportive research culture, has well-established resources and infrastructure to set up a pilot pathway and is keen to enhance what they can offer.

Professor Stephen Leeder described the Sydney Health Partners Advanced Health Research and Translation Centre, which consists of collaborations between Local Health Districts, Specialty Networks, Medical Research Institutes and the University of Sydney. One of the main aims of the Advanced Health Research and Translation Centre is to remove barriers to clinical research and research training by streamlining processes, including governance and facility-sharing. Piloting training pathways in this type of setting would be highly instructive.

The Australian Academy of Health and Medical Sciences and mentoring

Professor Ian Frazer described the vision and mission of the recently established AAHMS. This Academy has a strong senior mentorship programme that explicitly aims to help sustain the medical research workforce into the future. Furthermore, the AAHMS contributes to discussions on the research priorities in health and medical sciences with government. It is anticipated that the AAHMS will become a strong advocate for the establishment of training pathways for clinical academics, and may help lead the way to the development of mentorship programmes at all stages of the clinical academic training and career pathway. The AAHMS, Australia’s newest learned Academy, has as its mission to promote health and medical research and its translation to enable a healthier community.

The National Health and Medical Research Council and funding

It is recognised that the successful implementation of defined clinical academic training pathways will require the engagement of several government organisations, including the National Health and Medical Research Council. The NHMRC representative, Dr Richele Rasmussen, presented the opportunities offered by Australia’s largest research funding body. A focus of NHMRC is to support the translation of health and medical research into clinical practice, health policy and healthcare delivery. Dr Rasmussen also noted that commercialising outputs from research is another form of research translation. NHMRC supports such translation through a number of funding mechanisms, including the Translating Research into Practice Fellowships, Practitioner Fellowships and through the Advanced Health Research and Translation Centre initiative. The rate of successful funding across the different NHMRC
fellowship schemes is shown in Table 2, and the proportion of funding allocated to medical graduates is shown in Table 3. These data are lacking detail on the specifics of the funding distribution in regards to clinical academics. This is an area that requires further data collection to enable more rigorous understanding of the current and required support for this workforce. The Working Group noted opportunities to develop more funded positions for medical graduates and to look for ways to integrate these into clinical academic pathways.

The Medical Research Future Fund (MRFF) funding was discussed at the summit. It presents an important opportunity that is distinct from the funding available through the NHMRC. What is clear is that funding will be required to implement a training pathway for clinical academics in Australia and New Zealand. More information is required about how the government plans to allocate the MRFF, and it is important to make a strong case for the importance of a well-trained and sustainable clinical academic workforce, which is critical to the innovation required to improve clinical outcomes and address healthcare expenditure.

Model implementation and the way forward

These presentations confirmed that many Australian and New Zealand healthcare organisations have made significant investment and progress in developing training pathways for clinical academics. Sustaining the clinical academic workforce and ensuring their ongoing contributions to research, health outcomes and service delivery is a critical issue. The Working Group considers that the major barrier to addressing this issue is the lack of an integrated, defined and funded approach to training. However, the Working Group also sees significant potential for the current models of training to be standardised and for them to be replicated in other organisations. The provision of such a training pathway will require the allocation of federally funded grants specifically for clinical academics. The Working Party has requested that this initiative be included on the priorities for the MRFF, and is continuing to advocate for this funding while this decision is being made. Federal funding will also be sought for data collection on clinical academics, to ensure that the implementation of pathways has a beneficial effect. To progress the implementation of a pilot pathway, the Working Party is convening a meeting in early 2017 of organisations and jurisdictions that are willing to support and fund such a training pathway. This meeting will be by invitation only of those stakeholders who are already working closely with the Working Party. Once the success of a pilot pathway is demonstrated, additional sites can be incorporated. The key stages of the training pathway have been identified as the following: medical student, intern and pre-vocational doctor, vocational trainee, post-doctoral/early fellowships and definite appointment. Key enablers for developing an integrated and defined clinical academic training pathway would need to include meaningful mentoring programmes, role modelling, profiling successful clinical academics and their institutions and strategic funding for more training positions and administrative support.
Conclusions

The engagement by key stakeholders, including representatives from government, major funding bodies, universities and health translation centres, has been vital for creating an understanding of how best to move forward and to build momentum. The future goals and an action plan for the Working Party on Clinical Academic Pathways were summarised by Professor John Windsor, in closing. These included: (i) profiling successful clinical academics and institutions in the media and within medical schools; (ii) defining stages in the clinical academic training pathway drawing from current examples; (iii) publishing data on the value of clinical academics to the healthcare system; (iv) enlisting institutions into pilot training pathways for clinical academics at some or all stages; and (v) implementing a formal mentoring programme, possibly in association with key stakeholders, including representatives from government, major funding bodies, universities and health translation centres, has been vital for creating an understanding of how best to move forward and to build momentum. The future goals and an action plan for the Working Party on Clinical Academic Pathways were summarised by Professor John Windsor, in closing. These included: (i) profiling successful clinical academics and institutions in the media and within medical schools; (ii) defining stages in the clinical academic training pathway drawing from current examples; (iii) publishing data on the value of clinical academics to the healthcare system; (iv) enlisting institutions into pilot training pathways for clinical academics at some or all stages; and (v) implementing a formal mentoring programme, possibly in association with the Australian Academy of Health and Medical Sciences.

The summit concluded with Professor David Watters, President of RACS, and Professor Nicholas Glasgow, President of Medical Deans Australia and New Zealand, emphasising the importance of this initiative and the themes of the summit. They gave strong endorsement to the plans as outlined, especially around the development of models for research funding and remuneration. This will need to be considered in more depth at the next summit. In addition, the next steps must focus on defined pilot pathways in willing institutions in Australia and New Zealand, identifying and engaging key government representatives in research and education who will contribute to this initiative, and advocating increased funding for the recruitment, training and retention of the clinical academic workforce.

Acknowledgements

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ORIGINAL ARTICLES

Is it all about price? Why requests for government subsidy of anticancer drugs were rejected in Australia

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Key words
anticancer drugs, health technology assessment, drug subsidisation, decision making, cost-effectiveness.

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Abstract

Background: Australians access anticancer drugs predominantly through the Pharmaceutical Benefits Scheme (PBS).
Aim: To determine why the Pharmaceutical Benefits Advisory Committee (PBAC) rejects submissions to list anticancer drugs on the PBS.
Methods: We reviewed publicly available information about submissions made to the PBAC for PBS listing of anticancer drugs from 2005 to 2014. Submission characteristics, including clinical and economic evidence, PBAC recommendations, and the reasons offered for rejection were recorded. Two reviewers independently categorised the reason for rejection offered by the PBAC. Logistic regression was used to determine submission characteristics associated with rejection.
Results: We identified 213 submissions for 110 unique indications of 60 anticancer drugs. The overall rejection rate was 56% (119/213). Of the 110 indications assessed, 69% (76/110) were rejected at least once. The annual rejection rate ranged from 50 to 73% with little evidence of a trend over time ($P = 0.2$). Submission characteristics strongly associated with rejection in multivariable analysis included: PBAC judged the clinical evidence to be problematic or uncertain ($P < 0.001$); PBAC judged the economic evidence to be problematic or uncertain ($P < 0.001$); and, inactive comparator used ($P < 0.001$). The most frequent reasons for rejection offered by the PBAC was ‘inadequate cost-effectiveness or drug price too high’ (75/109, 69%).
Conclusions: Inadequate cost-effectiveness and PBAC uncertainty about the clinical and economic evidence were the most frequent reasons for rejection. Clarity of information about PBAC deliberations and their reasons for rejection are important for patients and doctors grappling with decisions about the use of expensive unfunded anticancer drugs.

Introduction

The Australian Pharmaceutical Benefits Scheme (PBS) is a multibillion dollar, government-funded, national drug formulary, which subsidises the cost to patients of listed prescription drugs, including anticancer drugs.1 Submissions for listing a drug on the PBS are prepared by a sponsor, usually a pharmaceutical company, and assessed by the Pharmaceutical Benefits Advisory Committee (PBAC) using the following criteria: safety and effectiveness; cost-effectiveness and budget impact; certainty of the evidence; and, degree of clinical need.2

Submissions to the PBAC fall under two broad categories – major or minor. A major submission requires an economic evaluation and includes submissions to list new drugs on the PBS or to make substantial changes to an existing listing. A submission can be classified as minor if it is a resubmission without substantiative changes (e.g. a price reduction only); or, if the purpose

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of the submission is to make minor changes to an existing listing (e.g. the addition of a new strength).2

The type of economic evaluation required for a major submission depends on the therapeutic claim put forward. If the claim is superiority to the standard of care, then the sponsor will usually submit a cost-effectiveness analysis. If the claim is therapeutic equivalence or non-inferiority, then a cost-minimisation analysis is sufficient. These analyses are required to help the PBAC appraise the clinical effect and cost of the new drug relative to the current standard of care.

After assessing a submission, the PBAC can recommend that a drug be listed on the PBS, reject the submission for listing or defer its decision. A rejected submission can be reconsidered if new evidence is provided.3 The PBAC first announces its recommendations on the website of the Department of Health, and subsequently provides more details about the rationale underpinning these recommendations as public summary documents (PSD).4

Understanding the rationale for rejections of submissions to list anticancer drugs on the PBS is important to those affected by cancer and their doctors. A rejection for listing will often make a new drug unaffordable to all, but those with the resources needed to cover the substantial treatment costs. The details are also important for oncologists to have informed discussions with their patients about the value and costs of unfunded anticancer drugs.3–7

The main purpose of this study was to determine the reasons why the PBAC rejected submissions to list anticancer drugs on the PBS. We sought to determine the characteristics of rejected submissions for listing of anticancer drugs, the reasons offered for rejection by the PBAC, and if there were changes over time in the rate of rejection.

Methods

We reviewed all submissions made to the PBAC for listing of anticancer drugs on the PBS from July 2005 to July 2014. Details about these submissions were identified from PSD and brief summaries of outcomes (BSO) published on the PBS website.8,9 July 2005 was chosen as the start date as this was the first time PSD was made available. We reviewed both major submissions, which were always reported in PSD and BSO, and minor submissions, which were sometimes only reported in BSO.

We included submissions about anticancer drugs used for the treatment of solid cancers (including non-melanoma skin cancers), haematological cancers and bone metastases. We excluded submissions about drugs used for supportive care during treatment (e.g. anti-emetics and immunomodulating drugs), submissions requesting simultaneous assessment of more than two indications for a single drug, and minor submissions when clinical or economic data were not considered. Different indications identified from the same PSD or BSO were considered as separate submissions.

The set of characteristics extracted from submissions was developed from characteristics previously reported as being influential in the decision making of the PBAC and similar health technology assessment bodies in other countries.2,10–13 The characteristics included information submitted to the PBAC (e.g. clinical trial evidence of an overall survival benefit), judgements or opinions of the PBAC that were reported in PSD, and recommendations made by the PBAC (see Supporting Information Table S1 for full list of characteristics). Definitions of characteristics and possible responses were specified before data were extracted. Recommendations made by the PBAC were dichotomised as either a recommendation for listing or a rejection (including rejections and deferrals).

The reasons for rejection offered by the PBAC, as distinct from the characteristics of the submission, were exclusively extracted from the final section of the PSD that specifically records this information. Reasons for rejection were extracted verbatim, and then later categorised after the initial data entry was completed. Two of the authors extracted all data from submissions independently and resolved any disagreements by consensus.

Standard descriptive statistics were used to summarise the characteristics of all submissions, and the reasons for rejection offered by the PBAC. An association between the submission year and likelihood of rejection was tested using a logistic regression. The logistic regression model was fitted using generalised estimating equations to account for repeated submissions for the same drug and indication. Individual characteristics were evaluated for univariable associations with rejection using logistic regression (fitted with generalised estimating equations). Characteristics that were statistically significant on univariable analysis, from major submissions, and not explicit judgements of sponsor claims (e.g. acceptance of efficacy claim) were then evaluated in a recursive partitioning analysis. The subset of these characteristics that had wide applicability across the major submissions was included in a multivariable logistic regression model. Backward elimination was used to select variables that were independently significant at \( P < 0.05 \). Recursive partitioning analysis was performed with the rpart package in R (R Foundation for Statistical Computing, Vienna, Austria). All other statistical analyses were performed with SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).
Results

We identified 213 evaluable submissions for PBS listing of anticancer drugs between July 2005 and July 2014, 182 in both PSD and BSO and 31 in BSO alone. Of the 213 submissions, 154 (72%) were a major submission and 59 (28%) were a minor submission. All major submissions were reported in a PSD compared with just under half (28) of minor submissions. There was a similar proportion of resubmissions (113, 53%) and initial submissions (100, 47%), and 86 (40%) submissions were for anticancer drugs not already listed on the PBS for another indication.

The 213 submissions covered 110 unique indications for 60 anticancer drugs. Of the 110 indications assessed, the most common tumour types were breast cancer (19, 17%), non-small cell lung cancer (12, 11%) and colorectal cancer (12, 11%); 90 (82%) were for treatment with non-curative or palliative intent; and, 36 (33%) required testing for a biomarker or treatment target as a condition of use.

The rejection rate for all submissions was 119 of 213 (56%), and for the subset of submissions reported in a PSD, it was 109 of 182 (60%). Of the 110 indications assessed, 76 (69%) were rejected at least once, and 31 (28%) were rejected more than once (Fig. 1). By October 2015, of the 110 indications assessed over the study period, 91 (83%) were listed on the PBS and 19 (17%) remained unlisted. The rejection rate by calendar year from 2005 to 2014 ranged from 50 to 73% with little evidence of a trend over time ($P = 0.2$) (Fig. 2).

Results of the univariable logistic regression analyses used to identify submission attributes associated with rejection are shown in Table 1. Submissions in which the PBAC did not accept the sponsors’ comparator or efficacy claims were strongly associated with rejection, as were submissions in which the PBAC judged the clinical evidence problematic or uncertain. Rejection was also associated with submissions that had indications with a palliative intent, inactive comparators and base case incremental cost-effectiveness ratios (ICERs) > $45 000/quality-adjusted life year (QALY). Only 1 of 20 submissions with an ICER range > $75 000/QALY was recommended for listing on the PBS. The one submission with an ICER range < $15 000/QALY was rejected. All 10 submissions that the PBAC judged to have an inappropriate comparator were rejected.

Table 2 shows the results of our multivariable logistic regression analysis. A PBAC judgement of problematic or uncertain clinical evidence and an inactive comparator had the strongest association with rejection. The results of the recursive partitioning analysis applied to characteristics that were significantly associated with rejection in the univariable analysis are illustrated in Figure 3. The characteristic that best discriminated between rejection and a recommendation for listing was PBAC judged the clinical evidence problematic or uncertain – 81% (73/90) of major submissions with this characteristic were rejected, versus 39% (23/64) without this characteristic. Of the 64 major submissions without this characteristic, an ICER > $45 000/QALY was the strongest discriminator between a recommendation for listing and rejection. Major submissions most likely to be rejected were those when the PBAC judged the clinical evidence problematic or uncertain and an inactive comparator was used (24/25, 96%).

Table 3 summarises our categorisation of the reasons for rejection offered by the PBAC. Multiple reasons were documented for nearly all submissions that were rejected (101/109, 93%); the most frequent number of reasons per rejection was 3 (27/109, 25%). The reason for rejection that we categorised as most frequent was cost-effectiveness was inadequate or the drug price too high (75/109, 69%).
Table 1 | Univariable logistic regression analyses of the associations between each individual submission characteristic and rejection

<table>
<thead>
<tr>
<th>Submission characteristic</th>
<th>Reject (n [%])</th>
<th>Approve (n [%])</th>
<th>Total</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information submitted to the PBAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listing request‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New listing</td>
<td>54 (63)</td>
<td>32 (37)</td>
<td>86</td>
<td>0.11</td>
</tr>
<tr>
<td>Extend existing listing</td>
<td>65 (51%)</td>
<td>62 (49%)</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Submission type‡</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Initial submission</td>
<td>64 (64%)</td>
<td>36 (36%)</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Resubmission</td>
<td>55 (49%)</td>
<td>58 (51%)</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Treatment intent</td>
<td></td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Curative/adjuvant</td>
<td>10 (33%)</td>
<td>20 (67%)</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Palliative</td>
<td>99 (65%)</td>
<td>53 (35%)</td>
<td>152</td>
<td></td>
</tr>
<tr>
<td>Test required before drug can be used</td>
<td></td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Yes</td>
<td>41 (65%)</td>
<td>22 (35%)</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>68 (57%)</td>
<td>51 (43%)</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Comparator type</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Active</td>
<td>68 (57%)</td>
<td>51 (43%)</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Inactive (e.g. placebo, best supportive care)</td>
<td>30 (86%)</td>
<td>5 (14%)</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Type of trial evidence submitted</td>
<td></td>
<td></td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>Direct comparison trial(s) only</td>
<td>43 (67%)</td>
<td>21 (33%)</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Indirect comparison trials included</td>
<td>55 (62%)</td>
<td>34 (38%)</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Evidence of an overall survival benefit</td>
<td></td>
<td></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (70%)</td>
<td>16 (30%)</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32 (60%)</td>
<td>21 (40%)</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Type of economic analysis</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Cost-effectiveness analysis and/or cost-utility analysis</td>
<td>90 (66%)</td>
<td>47 (34%)</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>Cost-minimisation analysis; other</td>
<td>17 (41%)</td>
<td>24 (59%)</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>ICER (cost/QALY)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤$45 000/QALY</td>
<td>12 (41%)</td>
<td>17 (59%)</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>&gt;$45 000/QALY</td>
<td>62 (78%)</td>
<td>18 (23%)</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Estimated impact on the PBS budget per year</td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>&lt;$10 million</td>
<td>55 (59%)</td>
<td>38 (41%)</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>≥$10 million</td>
<td>41 (76%)</td>
<td>13 (24%)</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>PBAC judgements of sponsor claims</td>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Comparator claim</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accepted</td>
<td>69 (58%)</td>
<td>50 (42%)</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Partially accepted; rejected</td>
<td>25 (89%)</td>
<td>3 (11%)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Efficacy claim</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Accepted</td>
<td>39 (48%)</td>
<td>42 (52%)</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Partially accepted; rejected; unclear</td>
<td>59 (81%)</td>
<td>14 (19%)</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Toxicity claim</td>
<td></td>
<td></td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>Accepted</td>
<td>42 (67%)</td>
<td>21 (33%)</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Partially accepted; rejected; unclear</td>
<td>56 (62%)</td>
<td>35 (38%)</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Other judgements made by PBAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBAC judged clinical evidence problematic or uncertain</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>73 (81%)</td>
<td>17 (19%)</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25 (39%)</td>
<td>39 (61%)</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>PBAC judged economic evidence problematic or uncertain</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>75 (76%)</td>
<td>24 (24%)</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22 (41%)</td>
<td>32 (59%)</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>PBAC judged there to be a high clinical need</td>
<td></td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>Yes</td>
<td>32 (73%)</td>
<td>12 (27%)</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>66 (60%)</td>
<td>44 (40%)</td>
<td>110</td>
<td></td>
</tr>
</tbody>
</table>

†Logistic regression fitted with GEE. ‡No PSD is required to determine these variables and so applicable to all 213 submissions. All other variables were determined from the 182 submissions with a PSD. GEE, generalised estimating equations; ICER, incremental cost-effectiveness ratio; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PSD, public summary document; QALY, quality-adjusted life year.

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Discussion

Our study has found several important factors contributing to rejection by the PBAC of submissions for listing of anticancer drugs. The importance of inadequate cost-effectiveness was demonstrated, amongst applicable submissions, by the association between rejection and an ICER > $45 000/QALY in both the univariable analysis and the recursive partitioning analysis. Inadequate cost-effectiveness or drug price too high was also the most

Table 2 Multivariable logistic regression analysis of the associations between submission characteristics and rejection

<table>
<thead>
<tr>
<th>Submission characteristic</th>
<th>Univariable†</th>
<th></th>
<th></th>
<th>Multivariable†</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>P value</td>
<td>OR</td>
<td>95% CI</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>--------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>PBAC judged clinical evidence problematic or uncertain (yes vs no)</td>
<td>6.76</td>
<td>3.24–14.1</td>
<td>&lt;0.001</td>
<td>8.47</td>
<td>3.25–22.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comparator type (inactive vs active)</td>
<td>4.29</td>
<td>1.66–11.1</td>
<td>0.003</td>
<td>10.8</td>
<td>3.20–36.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PBAC judged economic evidence problematic or uncertain (yes vs no)</td>
<td>4.54</td>
<td>2.21–9.30</td>
<td>&lt;0.001</td>
<td>4.35</td>
<td>1.82–10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated impact on the PBS budget per year ($&lt;10 million vs $≥10 million)</td>
<td>2.17</td>
<td>1.05–4.55</td>
<td>0.037</td>
<td>4.17</td>
<td>1.56–11.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Treatment intent (palliative vs curative/adjuvant)</td>
<td>3.85</td>
<td>1.47–10.0</td>
<td>0.006</td>
<td>2.70</td>
<td>1.00–7.14</td>
<td>0.05</td>
</tr>
<tr>
<td>Type of economic analysis (cost-effectiveness and/or cost-utility vs cost-minimisation or other)</td>
<td>2.68</td>
<td>1.26–5.70</td>
<td>0.010</td>
<td>NS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ICER ($&gt;45 000/QALY vs $≤45 000/QALY)</td>
<td>7.70</td>
<td>2.9–20.4</td>
<td>&lt;0.001</td>
<td>NA‡</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

†Logistic regression fitted with GEE. ‡Not included as a candidate variable in principal analysis as only applicable to 57% (88/154) of major submissions.

In a sensitivity analysis when it was included, an ICER > $45 000/QALY was significantly associated with rejection, as were: PBAC judged clinical evidence problematic or uncertain; PBAC judged economic evidence problematic or uncertain; and an inactive comparator. CI, confidence interval; ICER, incremental cost-effectiveness ratio; NA, not applicable; NS, not significant; OR, odds ratio; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; QALY, quality-adjusted life year.

Figure 3 Recursive partitioning analysis applied to characteristics from major submissions associated with rejection on univariable analysis.
frequent reason for rejection based on our categorisation of the reasons for rejection offered by the PBAC. PBAC uncertainty about the clinical and economic evidence was also an important factor. PBAC judgements of uncertain or problematic clinical evidence, and uncertain or problematic economic evidence, were submission characteristics significantly associated with rejection in our multivariable logistic regression analysis and were frequently offered as reasons for rejection based on our categorisation. The recursive partitioning analysis also demonstrated that a PBAC judgement of uncertain or problematic clinical evidence best discriminated between a recommendation for listing and rejection.

We were surprised to find that submissions for drugs without a demonstrated survival benefit over their nominated comparator were no more likely to be rejected. At first glance, this suggests the erroneous conclusion that survival benefits are unimportant to the PBAC. Recommendations for listing in the absence of a demonstrated survival benefit may have been based on strong evidence from important surrogate end-points, such as progression-free survival or because of demonstration of non-inferiority with a drug already proven effective. For example, recommendations for erlotinib and gefitinib in the treatment of non-small cell lung cancer with driver mutations of the gene for epidermal growth factor receptor, were based on improvements in important surrogate end-points, progression-free survival and quality of life, in comparison with chemotherapy using a platinum-based doublet, the prior standard of care. Pazopanib was recommended for listing for the treatment of metastatic renal cell carcinoma based on evidence of non-inferiority in comparison with sunitinib, which had already been PBS listed for this indication. Such submissions will not have been recorded as demonstrating evidence of a survival benefit in our study, even if there is available evidence for the anticaner drugs in question against placebo or other unnominated comparators.

Conversely, some submissions for listing drugs with a demonstrable survival benefits were rejected by the PBAC. Examples in our study include the first submission for listing bevacizumab in combination with chemotherapy as first-line treatment of metastatic colorectal cancer, and the first submission for listing abiraterone in metastatic, castration-resistant prostate cancer, following treatment with chemotherapy. Robust evidence of a substantial survival benefit may justify a high asking price, but a higher asking price will reduce cost-effectiveness, perhaps resulting in rejection. It is important to note that most submissions for listing anticaner drugs with a demonstrable survival benefit, including the previous examples, were eventually approved. Of the 19 indications assessed in our study that remained unlisted in October 2015, only five were supported by statistically significant survival benefits.

The main strength of this study is its comprehensive review of all submissions made to the PBAC regarding the PBS listing of anticaner drugs since PSD became available up until July 2014. This is timely given the growing community concern about the issue of high cost anticaner drugs and a recent Senate Inquiry into access to innovative cancer drugs in Australia. Inclusion of all PBAC recommendations since 2005, not just those reported in PSD, ensures that the rejection rate is not overestimated. Independent data extraction by two investigators also contributes to the credibility of our results. This study builds on our previous study by exploring the reasons the PBAC rejects anticaner drugs for listing. Other studies, including our previous one, were not limited to analysis of anticaner drugs, but also found that the frequency of rejections by PBAC was increased by uncertainty, inadequate cost-effectiveness and health budget impact.

<table>
<thead>
<tr>
<th>Reason for rejection</th>
<th>Rejected submissions (n = 109)</th>
<th>Number of submissions in which reason was offered</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBAC stated the cost-effectiveness was inadequate or the drug price too high</td>
<td>75</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>PBAC judged economic evidence problematic or uncertain</td>
<td>73</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>PBAC stated they were uncertain about the cost-effectiveness</td>
<td>64</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>PBAC judged clinical evidence problematic or uncertain</td>
<td>61</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>PBAC judged the drug’s nominated clinical place and/or comparator problematic or uncertain</td>
<td>41</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Supplementary data or analysis was required by the PBAC</td>
<td>22</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>PBAC had concerns about the PBS or health budget impact</td>
<td>16</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>PBAC had concerns about the safety or toxicity of the drug</td>
<td>11</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>PBAC had concerns about the test required as a condition of use</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Other miscellaneous reasons</td>
<td>17</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme.

Table 3  Our classification of reasons offered by the PBAC for rejecting submissions for listing on the PBS
The main limitations of our study stem from its reliance on publicly available information. PSD aims to provide the public information about PBAC recommendations, but they arose as a result of requests for more transparency about the basis of subsidy of pharmaceuticals to Australians, as part of the Australian-United States Free Trade Agreement. The PBAC is governed by the National Health Act, therefore content published in PSD is subject to Commonwealth law, and is negotiated by the PBAC and the sponsor to protect commercial confidentiality. As a result, pertinent information considered by the PBAC may be omitted.

Uncertainty about the cost-effectiveness of a new anticancer drug reduces the likelihood that it will be publicly funded, especially if the price of a new anticancer drug is high and would result in substantial total expenditure. Sources of uncertainty for the PBAC include aspects of clinical trial design that obscure the magnitude of benefit (e.g. crossover from control group to experimental treatment); applicability of submitted trial evidence to the Australian context (e.g. inappropriate comparator); and assumptions or flaws in the economic models submitted (e.g. extrapolation of trial results beyond the duration of follow-up). PSD for drugs rejected by the PBAC because of ‘uncertainty’ are often unclear about whether the ‘uncertainty’ is about the benefits, the costs, the cost-effectiveness or some other unspecified consideration. We recommend that PSD should explicitly specify the areas and reasons for uncertainty and how these uncertainties contributed to the PBAC’s recommendation.

Despite challenges faced by the PBAC, such as high prices and uncertain benefits, our study has not demonstrated clear evidence of an increasing linear trend over time in the rejection rate for anticancer drugs. The rejection rate of initial submissions was nevertheless greater in the second half of the study period compared to the first. Policy arrangements that promote rapid access to new anticancer drugs to allay the concerns of patients and doctors, while ensuring value for money is still considered, should be encouraged.

Funding decisions in health systems that fund anticancer drugs significantly affect the practice of medical oncologists and the anticancer drugs that are accessible to patients. Surveys demonstrate that patients want information about the availability of high cost, unfunded drugs, and may feel that it is unfair that these drugs are not funded. Understanding that a drug was rejected because of doubts about its efficacy, rather than its high cost, might help patients in deciding whether or not to pursue an expensive treatment.

Cancer is sometimes paid special attention by health technology assessment agencies and reimbursement authorities. For example, a ‘Cancer Drugs Fund’ was created in the United Kingdom to provide access to anticancer drugs, which were increasingly receiving negative recommendations from the National Institute for Health and Care Excellence. Our study of recommendations from 2005 to 2008 showed that the PBAC was equally likely to recommend or reject drugs for cancer versus other indications, but recommendations since 2008 warrant analysis. Further research is also needed to determine the extent to which the criteria used by PBAC to value new anticancer treatments match those of the wider community.

**Conclusion**

The rapidly rising cost of new anticancer drugs has made rigorous determination of their value an urgent and important priority. Rejection of a submission for listing on the PBS moves the problem from the domain of health policy to that of individual clinical decision making. This makes it even more important that the PBAC provide clear information about its deliberations and the reasons for rejection or recommendation for listing of expensive new anticancer drugs. Better information about the reasons for rejection should help patients and doctors make more informed decisions about the use of expensive unfunded treatments.

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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. Full list of characteristics extracted from publicly available information about submissions made to the PBAC for PBS listing of anticancer drugs.
Perceptions of cancer of unknown primary site: a national survey of Australian medical oncologists

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Abstract

Background: Despite being the sixth most common cause of cancer death in Australia, cancer of unknown primary (CUP) site remains poorly understood.

Aims: To describe practices relating to the diagnosis, investigation, classification, communication and management of CUP among medical oncologists.

Methods: We invited all members of the Medical Oncology Group of Australia to participate in a national, anonymous online survey about CUP. The survey collected data regarding diagnosis acceptance, diagnostic tests, treatment protocols and communication practices around the diagnosis of CUP.

Results: Three hundred and two oncologists were invited and 86 (28%) completed the survey. Eighty (93%) respondents were directly involved in the assessment of patients with CUP. Eighty-five (99%) respondents were prepared to make a diagnosis of CUP if, after appropriate diagnostic tests, the primary location could not be ascertained. Eighty-three percent would assign a primary site to obtain Pharmaceutical Benefits Schedule funding of medical therapy. Sixty-two percent did not have a specific treatment protocol designed for CUP. The majority of oncologists used serum tumour markers and computed tomography scans in the initial work-up, while 43% indicated they would use a positron emission tomography scan in the majority of cases. The majority would arrange mammography in female patients. Thematic analysis of responses to open-ended questions about how CUP is described identified little consistency in the language being used.

Conclusion: The approach to diagnosis, investigation and management of CUP by medical oncologists in Australia is variable. Many preferred to estimate the primary site and treat accordingly. Pharmaceutical Benefits Schedule restrictions may encourage the practice of ‘best guessing’.

Introduction

Failure to determine the site of origin of a cancer, so called cancer of unknown primary site (CUP), has been recognised as a distinct diagnostic entity for over 30 years.1 There are no distinguishing clinical signs or symptoms to denote the primary location of the cancer.

Epidemiologic studies have reported that CUP represents between 2 and 5% of all cancer diagnoses.2,3 In 2011, approximately 2800 Australians received a new diagnosis of CUP. This was the 12th most commonly diagnosed cancer in men and 11th in women.4 CUP is typically associated with a poor survival, and in 2012 it was the sixth most common cause of cancer-related death.4

Recent epidemiological data from the United States and Australia indicate that the incidence of CUP has declined.4,5 An analysis of the Surveillance, Epidemiology and End Results database in the United States...
revealed a proportional decline in CUP since 2007 to less than 2% of all cancer diagnoses. This decrease may reflect changing clinical diagnostic criteria and reporting practices.

Poor acceptance or lack of acknowledgement of a diagnosis of CUP may contribute to an under-reporting of the diagnosis to cancer registries. While in recent years the utilisation of more sensitive radiological procedures, including magnetic resonance imaging, fine slice computed tomography (CT) scan and positron emission tomography (PET) scanning has increased the detection rate of primary cancers, for the majority of CUP cases the primary cancer remains elusive. Doubt regarding the utility and cost effectiveness of these diagnostic procedures for CUP remains, but they may be performed on an individual indication basis. Immunohistochemical staining of pathology slides has also helped clinicians in ascribing a probable site of origin. Most recently, the use of gene expression profiling to develop tissue of origin assays has increased the ability to assign the most likely primary site. Despite technological advancements and increased sophistication in the analysis and interpretation of these findings, there usually remains a margin of uncertainty.

Arguably, the diagnosis and management of CUP is one of the most difficult challenges in oncology. Overall, the prognosis for patients with CUP is poor. A recent population-based US registry analysis of adenocarcinoma of unknown primary site revealed only a marginal improvement in survival between 1973 and 2008. The diagnosis of CUP commonly confuses and frustrates patients, their carers and their doctors. The inability to identify a primary site may be seen as a failure of the diagnostic process. Moreover, patients understand that treatment is usually selected according to the site of origin of the malignancy. If a site is not identified, then patients may feel that accurate and optimal treatment selection is not possible.

In many parts of the world, including Australia, access to cancer therapies is regulated. In Australia, access to cancer therapies is funded by government through the public-access Pharmaceutical Benefits Scheme (PBS). The PBS enables subsidised access to relatively expensive cancer treatments for all Australians. Funding approval requires the doctor to gain authority to prescribe particular drugs for specified diagnoses and clinical situations. Consequently, oncologists may decide to assign an originating cancer site, so as to enable access to drugs to treat the CUP.

The aim of this study was to assess diagnosis acceptance, diagnostic tests and treatment protocols, as well as communication and documentation practices, among a representative sample of Australian medical oncologists.

Methods

Sample

A total of 302 members of the Medical Oncology Group of Australia, who comprise the majority of medical oncologists in Australia, was invited to complete an online survey.

Measures

The survey comprised 14 closed-response questions, and two open-ended questions and one categorical question with a comment option. The survey was pilot tested by the CUP steering committee coordinated by the Cancer Council NSW and the wording of items was altered in response to feedback. The survey evaluated oncologists’ understanding of CUP and assessed recognition of the diagnosis. The survey also explored the investigations and procedures commonly performed, the treatment protocols utilised and clinical practices, such as communication strategies in the management of CUP. In addition, we asked about the diagnostic assignment, particularly with reference to accessing cancer medication on the PBS, an Australian Commonwealth government-funded drug access programme. The open-ended questions were designed to explore the language medical oncologists used to describe CUP and how the diagnosis is communicated and discussed. The open-ended questions were ‘How do you describe or discuss a diagnosis with patients and families? Is CUP a term that you use? Please give a brief description’; and ‘Cancer of Unknown Primary is a difficult diagnosis to explain. How do you discuss it?’ A copy of the questionnaire is provided in the online Supporting Information Appendix S1.

Procedures

Members of the Medical Oncology Group of Australia were sent an invitation by email, inviting them to complete an online survey. The invitation was initially sent on March 2012 with a reminder email sent in May 2012. The survey was expected to take 10 min to complete.

Analysis

Descriptive statistics were used to summarise the survey data. A qualitative content analysis of the open-ended questions and of comments provided was also performed. The data were inserted into an Excel spreadsheet and two data coders (LG and PS) individually analysed to identify themes and sub-themes. The two
sets of categorisations were compared and disagreements discussed until agreement was reached.

**Results**

A total of 86 oncologists completed the survey (response rate 28%). Eighty of the respondents confirmed their direct involvement in the assessment of patients with CUP.

Participant demographics are presented in Table 1. Seventy-seven of the respondents were based in a metropolitan centre and 70 listed a public hospital or clinic as their principal place of work. The remaining 16 were based in private clinics.

Almost all survey respondents (99%) stated that they were prepared to make a final diagnosis of CUP if after appropriate diagnostic tests the primary site remained uncertain. However, when asked a different question that explored oncologists’ preference rather than willingness, 27% stated that they would prefer to provide a best guess of the primary site of the cancer, rather than diagnose CUP as a specific diagnostic entity, while a further 33% said that they would sometimes do this.

When asked specifically about accessing cancer therapies through the PBS, 83% (71/86) of respondents stated that they document a possible primary location of the cancer and define the cancer as such, to obtain PBS funding of a medical therapy for patients with CUP. Only 15 of the respondents said that they do not do this.

The vast majority (98%) disagreed ‘that all CUP cancers are the same entity’. Approximately, half (51%) responded ‘yes’ to the question ‘Do you have a specific diagnostic process for patients that present with CUP?’ and 62% (53/86) stated that they did not have a specific treatment protocol designed for patients with CUP at their institution.

The majority of medical oncologists used serum tumour markers and CT scan imaging in the initial diagnostic evaluation of suspected CUP, while 43% indicated they would use a PET scan in at least 50% of cases. Sixty-four percent stated that they would arrange mammography in more than 90% of cases of female patients with suspected CUP. Medical oncologists performed the following investigations in the majority (>50%) of CUP patients: tumour markers (88%), CT scan (98%), mammography in female patients (85%) and gastrointestinal endoscopy (60%). When medical oncologists were asked about investigations they perform in the vast majority (>90%) of CUP patients, only three investigations were included: tumour markers (67%), CT scan (91%), mammography in female patients (64%). The preferred investigations for CUP are depicted in Figure 1.

When asked about PET scan use to identify the primary site, 16% of respondents would arrange a PET scan in >90% of CUP cases, 41% of respondents would arrange a PET scan in >50% of CUP cases and the majority either do not utilise PET or use PET in fewer than 50% of cases.

**Theme 1: language to describe CUP**

**The primary tumour has regressed or is too small**

Clinicians that used the term CUP with their patients also often used the analogy of the primary tumour regressing and hence being undetectable. Several clinicians reported explaining to patients that ‘Primary (parent) appears to have regressed but metastases (children) have grown’, they ‘explain how in approximately 5% of cases we never can find the primary as it may be too small to visualise before it sends off metastatic cancer cells to other organs’ and ‘in a percentage of patients we cannot find the primary site as it may have regressed or is not able to be found by conventional diagnostic means’. A medical oncologist also reported using this scenario and further elaborating to explain, ‘there are a small number of patients where this happens and it is called “cancer of unknown primary”’.

**Uncertainty**

There is also considerable reference to uncertainty when explaining CUP to patients and family. It is a common subtheme used by medical oncologists both with and without the definitive use of the word CUP. Medical oncologists noted describing CUP as ‘Cancer that has
started in the body and spread but not sure where in the body it started’, ‘occasionally we remain uncertain of where cancer started even after all tests are complete’ and also ‘explain that [it is] uncertain as to where primary malignancy commenced and that sometimes this is the case with cancer’.

**Poor prognosis**

A minority of medical oncologists reported discussing the diagnosis in terms of its poor prognosis, for example: ‘whilst we can offer chemotherapy, it is not curable and prognosis is often in the realm of months rather than years’; and ‘this is a worse prognostic group with a particularly short survival’; ‘CUP is generally not curable except in occasional circumstances’. Another similar recorded response was: ‘I believe that true CUP is a syndrome with median survival 6 months no matter what you do’. Clinicians that did not use the term CUP also described the diagnosis in terms of the associated poor prognosis: ‘I provide a general description of the behaviour of the cancer and the poor prognosis’.

**‘Best guess’ diagnosis**

The use of a ‘best guess’ approach was also reported among clinicians who use the term CUP and those who do not. ‘No I don’t use CUP; I usually talk about my best guess primary’ and ‘CUP is a term that I do use, but I try to give information about the most likely primary site based on pathological findings’. There were several responses that incorporated a best guess in their description of a likely diagnosis when explaining CUP to their patients: ‘I divide the body into regions, discuss tissue diagnosis and exclude what we can as a primary’; ‘I provide a possible origin or most likely site of primary tumour’. Some responses demonstrated efforts to promote an understanding that this is a recognised common cancer type, I ‘do tell patients that CUP is a reality and more common than one might think’, ‘it is not unusual to have cancer spread without knowing where it has come from’, I ‘explain that is not uncommon’ and I ‘stress that it is an entity that accounts for up to 5% of cancer diagnoses’.

**Theme 2: treatment approaches**

**‘Best guess’ to guide treatment**

When discussing treatment options to CUP patients, a common subtheme was using the ‘best guess’ of the primary site to guide treatment choice. Medical oncologists reported that they ‘explain the uncertainty about diagnosis and best guess the treatment option’, ‘anti-cancer treatment, if appropriate, is based on best guess according to clinical pattern’ and the ‘need to treat with a best guess approach’. It was also reported that other clinical information is often used to guide this approach; I ‘discuss patient presentation, test results and outcomes and best fit chemotherapy for the situation’ and ‘options are based on the location of the disease and likely best fit pattern to determine treatment choice’. This approach indicates the use of best clinical judgement in the face of uncertainty. The ‘best guess’ is based on all available clinical, radiological and histopathological information.

**Broad-based therapy and treatments that ‘work’**

Medical oncologists also reported explaining the use of treatment effective against a broad spectrum of cancers as opposed to therapies typically used to treat particular...
cancer types: ‘There are a small proportion of cancers we are unable to find a primary for and we use therapies that are broad spectrum to give them the best result’; ‘there are drugs with broader spectrum that may cover a number of possibilities’ and ‘the initial site of the cancer can’t be found at this time, so we need to choose drugs that will work across a range of cancers’.

Some medical oncologists were positive about the effectiveness of therapy despite the inability to identify a primary; ‘we sometimes never find the origin of the cancer and it is usually widespread at diagnosis. It can respond well to treatment’. Some were also reassuring patients that there were alternative treatments if the initial treatment was ineffective; ‘it is still possible to provide treatment and that treatment can be changed to alternative treatment if it is not helping’.

**Theme 3: communication challenges**

**Clinician skill and time**

Clinician skill and allocating sufficient time were highlighted as important in overcoming communication challenges inherent in a CUP diagnosis. Medical oncologists reported the explanation of CUP to be a ‘discussion [that] is long and involved’, ‘not easily explained in a short comment’, and ‘takes great skill, experience, knowledge, empathy and time’.

**Patient ability to understand**

A clinician’s use of the term CUP was reported to be dependent on the patients’ level of understanding: I ‘sometimes use “CUP” terminology – depending on patient level of understanding’. It was also reported that a diagnosis of CUP was ‘not difficult to explain but difficult for patients and families to understand/accept’.

**Discussion**

CUP presents a wide diversity in diagnostic and treatment pathways. In the majority of cases, CUP represents a cancer (or a group of cancers) with multiple sites of involvement, displaying relatively aggressive biological behaviour and associated with a poor prognosis, but favourable prognostic subsets are recognised.19-22 Given the complexity around the diagnosis, and the negative connotations associated with terms of uncertainty, such as ‘unknown’, some experts in the field have recommended changing the diagnostic term to ‘Cancer of Complex Origin’.23 Our survey indicates that the language around CUP and medical oncologists’ approach to the initial diagnosis, investigation and management of CUP in Australia is variable. To our knowledge, this is the first attempt to understand how oncologists manage CUP clinically and the challenges that they face. We are not aware of any similar published data that we can compare our results to.

Many clinicians preferred the use of best clinical judgement to guess the primary site of the cancer and treat accordingly. In Australia, PBS restrictions to drug access appear to encourage the practice of ‘best guessing’ the primary site of cancer origin and assigning a diagnosis when requesting subsidised drug access through the PBS. The PBS restrictions otherwise prejudice CUP patients accessing potentially effective treatments. Acceptance of the CUP diagnosis was not universal among Australian oncologists. This may have implications regarding the accuracy of site-specific cancer registry data in Australia.

Variability was observed in the selection of the preferred initial investigations. CT scans, serum tumour markers, gastrointestinal endoscopy and mammography (for female patients) are investigations that oncologists said that they performed in the majority of cases. PET scanning is used in less than 50% of cases. A high degree of variability in the selection of investigations for the evaluation of CUP has previously been reported.1,24 In recent years, however, attempts to standardise the management of patients with CUP have been published based in the form of guidelines produced by the NCCN (National Comprehensive Cancer Network) and the European Society of Medical Oncology.25,26 These guidelines are based on evidence and consensus, but several areas remain contentious. The utility of PET in this setting, for example, remains debatable. Some authors have reported a high rate (>50%) of primary lesion detection through the application of fluorodeoxyglucose (FDG)-PET/CT scans.27,28 Others have reported a sensitivity of less than 50%.9,29 A recent study observed a high sensitivity, but low specificity in detecting the primary through PET in patients presenting with CUP in cervical nodes, and it is in this group that the guidelines recommend use of PET/CT.30

Most oncologists surveyed stated that their institutions did not have CUP-specific treatment protocols. This may be attributable to the absence of a globally accepted regimen. The approach to the treatment of CUP is evolving with the expectation that molecular analysis of the tumour will help identify genetic alterations for which there are specific targeted therapies. Indeed, a recent study reported a high rate of detectable genetic alterations in CUP specimens, the majority of which were found to be amenable to a molecular-targeted treatment strategy.31 Our survey did not specifically explore the utilisation of molecular testing in the assessment of CUP.
Limitations

A response rate of 28% is low and we acknowledge that there is likely to be bias in the responses obtained. Of the respondents within this sample, 94% of medical oncologists were involved in the assessment of patients during the diagnosis of CUP; therefore, data collected in this survey are biased toward oncologists that treat CUP. However, we believe that these are the only data available that assess diagnosis acceptance, diagnostic tests selected and treatment protocols used by medical oncologists. The assessment of the communication and documentation practices in relation to the CUP diagnosis also provides valuable insights into clinical practice and this has never been previously investigated or reported.

Conclusion

The survey highlighted that CUP is a diagnosis that is accepted by oncologists, but the majority would be prepared to provide a ‘best guess’ of the primary site in order to access drugs on the PBS and provide affordable treatment to patients. The management of patients with CUP is variable, as is the clinical presentation. The use of existing clinical practice guidelines may help Australian clinicians manage this complex malignancy.

Acknowledgements

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Supporting Information

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

Appendix S1. Cancer of unknown primary clinician survey.
Psychosocial screening and management of young people aged 18–25 years with diabetes

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Key words
diabetes mellitus type 1, young adults, psychology, evidenced-based practice.

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Abstract

Background: Routine psychosocial screening and management of people with diabetes is recommended.

Aims: To profile demographic, medical and psychosocial characteristics of young people with diabetes, and to develop a screening tool and care pathway for routine use.

Methods: Indices of diabetes control and recorded diabetes complications were complemented by psychosocial screening tools assessing psychological, diabetes specific and perceived stress (Kessler 10, Problem Area in Diabetes, Perceived Stress Scale), well-being (World Health Organization Well Being Index-5), disordered eating (Eating Disorder Risk Inventory-3 Risk Composite), compensatory behaviour questionnaire, social support (Multidimensional Scale of Perceived Social Support), resilience (Connor Davidson Resilience Scale – 2 item) and financial concerns. Service provision and demographic data were also collected. Diabetes and mental health clinicians then identified a subset of measures to use for routine screening along with care pathways.

Results: Psychosocial screening was well accepted. Participants (151) had suboptimal glycaemic control (glycated haemoglobin 8.0 interquartile range 1.8%/64 interquartile range 22 mmol/mol). Severe diabetes-related distress (Problem Area in Diabetes ≥40) was found in 19.4% and 26.0% reported difficulties managing healthcare costs. A mental health disorder was likely in 9.7%, whilst 23.4% had high Kessler 10 scores. Low World Health Organization Well Being Index-5 scores (≤13) were seen in 29.0%. Risk for an eating disorder (Eating Disorder Risk Inventory-3 Risk Composite) was 12.7%, whereas approximately 36.0% had disturbed eating behaviours.

Conclusion: Psychosocial screening of young adults with diabetes identified complex needs. A brief psychosocial screening tool and associated care pathways were developed for routine use in a young adult tertiary referral diabetes clinic. The tool assesses constructs, such as diabetes distress, depression, anxiety, well-being, hypoglycaemia-unawareness, fear of hypoglycaemia, social support, weight, shape and eating concerns and financial concerns. This will provide a longitudinal data source for further research to inform clinical practice.

Introduction

Diabetes guidelines recommend routine psychosocial assessment and treatment through a collaborative team approach, with psychological well-being and quality of life now considered an important treatment outcome of diabetes management in its own right.1,2 For successful implementation and follow through, the screening process must be effective in detecting vulnerable people, and the care pathways, services and resources offered must be acceptable to patients. Services are usually limited by financial and staffing constraints, therefore maximising staff skills and targeting individuals likely to benefit the most should be a focus of service provision.

Young people with diabetes have specific needs, as it is a period of significant change and challenges with respect to emotional and physical growth, and chronic illness management. During this phase, young people explore their identity with respect to moral, political and sexual orientations,3 they transition from school to higher...
education and/or employment, and from family-centric relationships to peer and employment-focused relationships. It can also be a period of risk taking with increased exposure to cigarettes, alcohol and illicit substances. Additionally, transition from paediatric to adult health services occurs and they can be lost to follow-up care. It is a time where glycaemic control can deteriorate and complications can result, as well as increased rates of depression, anxiety and eating disorders. Optimal diabetes management is intensive, and regular medical checks and multiple daily self-management tasks are required.

Identifying the mental health burden of this population as well as individual case identification is required to provide a comprehensive health service to this patient group. A multidisciplinary team approach seems indicated with evidence that this model is related to better glycaemic control, more support, lower diabetes-related distress and higher satisfaction with their diabetes care than those seeing a private endocrinologist, general practitioner or other provider.

We aim to investigate a representative sample of young people aged 18–25 years attending a large tertiary multidisciplinary diabetes clinic in a metropolitan area to report physical and a comprehensive array of psychosocial characteristics of this group, and explore relationships between these variables. Our wider objectives are to inform the deployment of non-medical members of the multidisciplinary team based on empirical evidence, and develop an abbreviated psychosocial screening tool for routine use along with a service model care pathway.

Methods

The multidisciplinary diabetes clinic is located in a purpose-built medical centre for young adults with chronic illness. The diabetes team includes endocrinologists, training registrars, diabetes nurse educators, dietitians and a clinical psychologist upskilled in type 1 diabetes management. The centre also provides a young adult support unit (psychiatrist, mental health nurse and psychologist) to which the diabetes team can refer.

All patients aged 18–25 years, who attended a routine clinic visit over a 20-week period, were invited to complete psychosocial screening measures. Exclusion criteria included those with a pre-existing mental health diagnosis or intellectual impairment and those who had difficulty reading or comprehending English. Ethics approval was obtained from Mater Health Services Human Research Ethics Committee.

Data collected from medical files included height, weight, most recent glycosylated haemoglobin, the type and duration of diabetes, insulin regimen and associated complications, including episodes of diabetes ketoacidosis (DKA) or severe hypoglycaemia (hypo) in the past 2 years. Utilisation of nursing and allied health services was documented. Regular clinic attendance was described as at least six clinic visits over a 2 year period. The young adult reported on ethnicity, living arrangements, marital status, employment, financial status and postcode (to determine metropolitan vs rural location).

Measures

Measures were completed by participants whilst waiting for the consultation, and took 20–30 min to complete. They included: The Problems Areas in Diabetes (PAID) (20 items) with scores ≥40 representing severe diabetes-related distress; and a score ≥30 representing significant diabetes-related distress; The Kessler 10 (K10; 10 items) assessing psychological distress, focusing on depression and anxiety symptoms, low levels of distress (10–15), moderate (16–21), high level (22–29) and very high (30–50) are defined; The WHO-5 Well-being Index (five items) assessing quality of life, with scores ≤13 indicative of low well-being, and scores <8 indicative of depression; The Eating Disorder Inventory Risk Composite (EDI-3RC) (25 items), assessing risk for an eating disorder with EDI-3RC scores ≥46, and a score in the typical or elevated clinical range on any scale is indicative of disturbed eating behaviours; and The Eating Disorder Compensatory Behaviour Questions (seven items) assessing the presence and frequency of binge eating, driven exercise, vomiting, laxative and diuretic use and insulin misuse. The Connor Davidson Resilience Scale (CD-2) (2 items), the Multidimensional Scale of Perceived Social Support (MSPSS) (12 items) and the Perceived Stress Scale (PSS) (10 items) were compared to USA normative data (non-diabetic), and four items assessed financial concerns.

Statistical analysis

Participant characteristics are presented using mean and standard deviation (SD) for normally distributed data (as assessed by the Shapiro–Wilk test) whilst median and interquartile range (IQR) presented for data not normally distributed. Percentages are used to describe categorical data. Students t-test has been used to compare normally distributed data and the Kruskal–Wallis and Mann–Whitney for non-parametric tests. Correlation of continuous variables performed with the Spearman’s rho test. Significance of association for categorical data was assessed using the Fishers Exact Test. Analysis was
done using IBM SPSS Statistics 22.0 for Windows and statistical significance was set at 0.05 for all analyses.

**Results**

Of the 172 eligible attendees, 164 (95.3%) participated, and 151 had attended clinic for more than a year (Fig. 1). Participants were predominantly Caucasian (93.4%; Asian 4.6%, African 0.7%, Middle East 0.7%), aged 21 (IQR 3), and 55.6% were female. The majority of participants were single (68.7%; defacto 26.0%, married 5.3%), lived with their parents (66.0%; with a partner 20.0%, alone 9.3%), most were engaged in some employment and/or study (76.5%, 49.0% respectively); a minority (6.7%) were unemployed (Table 1). Type 1 diabetes was predominant (98.7%), with a duration of 9 (IQR 8) years. Most were managed with intensive insulin therapy; 74.2% on multiple daily injections, and 22.5% insulin pump therapy. Body mass index (BMI) was 23.9 (IQR 4.2). Participants did not differ in age, BMI, duration of diabetes, insulin regimen or number of clinic visits from non-participants, however, non-participants had poorer glycaemic control (HbA1c 9.1% (IQR 2.2); 76.5 mmol/mol (IQR 24) vs 8.0 % (IQR 1.8); 64 mmol/mol (IQR 22) (P = 0.007)). Over the past 2 years, the median clinic visits were 6.0 IQR 3.

**Characterising physical and emotional health status**

Glycaemic control was suboptimal with the average HbA1c 8.0% (IQR 1.8), 64 mmol/mol (IQR 22) with significantly worse control in male participants (Table 1). Evidence of diabetes-related complications were seen with retinopathy in 6.6% of patients, peripheral neuropathy 4.6%, micro-albuminuria 13.2%, autonomic neuropathy 2% and peripheral vascular disease 2%. DKA rates over the past 2 years were 9.3%, and rates of a severe hypo were 18.0%. There were no significant gender differences in rates of DKA or hypos. The presence of a DKA episode over the past 2 years was associated with poorer glycaemic control (P = 0.004), however, there was no association with the occurrence of severe hypoglycaemia over the past 2 years.

Severe diabetes-related distress (PAID ≥ 40) was found in 19.4% of participants, with 31.6% having a PAID score ≥30. The K10 results indicated 9.7% had very high scores indicative of a mental health disorder, 23.4% had high scores and 29.0% had moderate scores. Of note, 11.3% of those with moderate or high K10 scores (≥22) did not exhibit significant diabetes distress (PAID score ≥30). WHO-5 scores indicating poor quality of life was reported in 29.0%.

Risk for an eating disorder (EDI-3RC) was 12.7%, whereas 35.8% had disturbed eating behaviours described as a high score on any of the EDI-3RC scales, and 38.7% reported an affirmative answer to at least one compensatory behaviour, for example, reducing or omitting insulin, binge eating or driven exercise. Of those with disturbed eating behaviours, 27.7% had PAID scores <30 and/or Kessler scores <22.

Mean PSS scores were 15.8 ± 7.6, the median social support (MSPSS) score was 6.0 IQR 1.7 and resilience score was 6.0 (IQR 2) (Table 1).

There was no significant association with age and psychosocial variables, however, females had significantly higher psychological distress and PSS scores (K10 P = 0.016 and PSS P = 0.025). Females also reported being less resilient, reported more eating disorders symptoms and lower well-being (CD-2 P = 0.008, EDI-3RC P = 0.001 and WHO-5 P = 0.002). There was a trend for female participants to feel more socially supported (MSPSS P = 0.064) (Table 1).

There was no association between the psychosocial measures with duration of diabetes, frequency of clinic visits and clinic distress.

Figure 1 Clinic attendees and recruitment during the study period.

* Study Participants: n = 151
** Non participants: n = 42
Table 1 Demographic, clinical and psychosocial characteristics of participants (n = 151)

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male</th>
<th>Female</th>
<th>Statistic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21.0 (3.0)</td>
<td>21 (3.0)</td>
<td>21 (4.0)</td>
<td>2444.0†</td>
<td>0.162</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>9.0 (8.0)</td>
<td>9 (8.0)</td>
<td>10 (9.0)</td>
<td>2653.0†</td>
<td>0.546</td>
</tr>
<tr>
<td>Insulin therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple daily injection</td>
<td>74.7%</td>
<td>79.1%</td>
<td>71.1%</td>
<td>0.007†</td>
<td>0.932</td>
</tr>
<tr>
<td>BD</td>
<td>2.7%</td>
<td>0%</td>
<td>4.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pump</td>
<td>22.7%</td>
<td>20.9%</td>
<td>24.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>23.9 (4.2)</td>
<td>24.1 (4.7)</td>
<td>23.5 (4.4)</td>
<td>2621.5†</td>
<td>0.471</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>8.0 (1.8)</td>
<td>8.4 (2.1)</td>
<td>7.9 (1.4)</td>
<td>2242.5†</td>
<td>0.042</td>
</tr>
<tr>
<td>HbA1c mmol/mol</td>
<td>64.0 (22.0)</td>
<td>68 (22)</td>
<td>63 (1.6)</td>
<td>2241.0†</td>
<td>0.041</td>
</tr>
<tr>
<td>DKA past 2 years</td>
<td>9.3%</td>
<td>7.5%</td>
<td>10.7%</td>
<td>2722.5†</td>
<td>0.495</td>
</tr>
<tr>
<td>Serious hypo past 2 years</td>
<td>17.9%</td>
<td>15.1%</td>
<td>20.2%</td>
<td>2361.0†</td>
<td>0.422</td>
</tr>
<tr>
<td>PAID (n = 144)</td>
<td>25.1 ± 19.4</td>
<td>22.5 ± 18.9</td>
<td>27.1 ± 19.6</td>
<td>−1.432§</td>
<td>0.154</td>
</tr>
<tr>
<td>Kessler 10 (n = 145)</td>
<td>19.5 ± 7.6</td>
<td>17.9 ± 6.9</td>
<td>20.8 ± 7.4</td>
<td>−2.345§</td>
<td>0.016</td>
</tr>
<tr>
<td>WHO-5 (n = 145)</td>
<td>60.8 ± 19.4</td>
<td>66.1 ± 18.1</td>
<td>56.5 ± 19.5</td>
<td>3.038§</td>
<td>0.003</td>
</tr>
<tr>
<td>EDI-3RC (n = 134)</td>
<td>31.6 ± 9.8</td>
<td>27.7 ± 7.1</td>
<td>34.7 ± 10.6</td>
<td>−4.555§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eating disorder CBQ</td>
<td>38.7%</td>
<td>30.6%</td>
<td>45.0%</td>
<td>2124.0†</td>
<td>0.083</td>
</tr>
<tr>
<td>Resilience scale (n = 148)</td>
<td>6.1 ± 1.5</td>
<td>6.5 ± 1.3</td>
<td>5.8 ± 1.6</td>
<td>2.805§</td>
<td>0.006</td>
</tr>
<tr>
<td>MSPSS (n = 144)</td>
<td>6.0 ± 1.7</td>
<td>5.8 ± 1.8</td>
<td>6.0 ± 1.6</td>
<td>−1.081§</td>
<td>0.282</td>
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<tr>
<td>PSS (n = 142)</td>
<td>15.8 ± 7.6</td>
<td>14.2 ± 7.4</td>
<td>17.1 ± 7.5</td>
<td>−2.259§</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Median (IQR). Means ± SD. Mann–Whitney U. †Kruskal–Wallis H test. ‡Independent samples test. BD, twice daily; BMI, body mass index; DKA, diabetes ketoacidosis; EDI-3RC, Eating Disorder Risk Inventory-3 Risk Composite; HbA1c, glycated haemoglobin; IQR, interquartile range; MSPSS, Multidimensional Scale of Perceived Social Support; PAID, Problem Area in Diabetes; PSS, Perceived Stress Scale; SD, standard deviation; WHO-5, World Health Organization Well Being Index.

Discussion

Results of psychosocial screening

We report the most comprehensive response rate and report of psychosocial screening in a tertiary young adult diabetes clinic. Psychosocial screening was embraced by this population as evidenced by the very high participation rate (99% of those approached). The abbreviated screening tool and care plan developed is designed to improve patient care and satisfaction with the service. Glycaemic control was suboptimal with only 16% meeting the target of ≤7%/53 mmol/mol. The rates of severe hypoglycaemia in the past 2 years (18.0%) was similar to previous reports,24.25 and along with a DKA rate of 9.3%, indicate further education is required to minimise such costly and preventable hospital admissions.

The lower rates of severe diabetes-related distress (19.4% PAID ≥40), than young adults from socially disadvantaged backgrounds (40%)11 or the MILES study (28%),25 could be due to socioeconomic advantage, the multidisciplinary team care, or other unidentified factors. Some results were aligned with previous findings. Approximately, one third had poor quality of life or psychological well-being, and/or high to very high levels of psychological distress, higher than Australian norms for 18–24 year olds (K10 high or very high ratings of 18.9%).11,26 High rates of disordered eating persist from adolescent years to adulthood.27 Financial concerns are not routinely asked in clinic consultations, but can impact significantly on glycaemic control, diabetes distress and psychological well-being.11 There are no comparative data for young adults with diabetes using the measures of resilience (CD-2), social support (MSPSS) and perceived stress (PSS).

Following on from the data collection, the diabetes clinicians and young adult support unit worked collaboratively to identify a subset of measures to use in routine screening and to develop care pathways (Fig. 2). The results of screening, team consensus and current evidence of treatment strategies for diabetes distress, comorbid mental health problems and for optimising
Figure 2 Psychosocial screening tool and care pathways for young people with type 1 diabetes. The tool consists of the complete questions from the Problem Areas in Diabetes (PAID) Questionnaire, Kessler 10, WHO-5 and additional questions.
The Mater Young Adult Health Centre Diabetes team are a multidisciplinary health service focusing on providing exceptional patient-centred care. The following questions will assist us in determining which allied health service you may benefit from. Completion of this form is optional.

Do you have particular concerns or questions that you would like to be addressed today?

1. 
2. 
3. 

Social Support for Life in general

<table>
<thead>
<tr>
<th></th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly agree</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>I can count on someone when things go wrong</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I can talk about my problems with someone</td>
<td></td>
<td></td>
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</tbody>
</table>

Your weight, shape and eating

On a scale of 1 to 5 where 5 is the best outcome:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>I am comfortable with my current weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I am comfortable with my body shape</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I am comfortable with my eating pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Financial concerns

<table>
<thead>
<tr>
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<th>No</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you have a Medicare Card?</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Do you have a NDIS Card?</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Do you have a Health Care Card?</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Do you have difficulty managing your living costs on your current income?</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Do you have difficulty managing your healthcare costs on your current income?</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Do you have private health insurance (independently or with your parent’s scheme)?</td>
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</tbody>
</table>

Hypoglycaemia (low blood glucose)

<table>
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<th></th>
<th>Not a problem</th>
<th>Slight problem</th>
<th>Moderate problem</th>
<th>Somewhat serious problem</th>
<th>Serious problem</th>
<th>Very serious problem</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>I feel that I can’t ever be safe from hypoglycaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Do your hypoglycaemia symptoms usually occur at a blood glucose level of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 or more mmol/L</td>
<td>Between 2.0-2.9 mmol/L</td>
<td>Less than 2mmol/L</td>
<td>I do not feel symptoms</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Your well-being

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>More than half the time</th>
<th>Less than half the time</th>
<th>Some of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I have felt cheerful and in good spirits</td>
<td>S</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>I have felt calm and relaxed</td>
<td>S</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>I have felt active and vigorous</td>
<td>S</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>I have felt up feeling fresh and rested</td>
<td>S</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>My daily life has been filled with things that interest me</td>
<td>S</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Care-pathway

<30
- No mental health concerns
- Mental health concerns

≥30
- No mental health concerns
- Mental health concerns

Usual care – MD team
- Credentiated Diabetes Educator
- Mental Health referral
- Mental Health referral if required.

Other considerations for all – refer to multidisciplinary team as appropriate and document results in chart:
- Social Support: If disagree, strongly disagree
- Weight, shape and eating: if score 1 or 2 (refer to dietitian/disordered eating protocol)
- Financial Concerns: No to Q 1, 2, 3 (if eligible) and 6, or Yes to Q 4 and 5
- Hypoglycaemia: slight problem or if 2.0-2.9mmol/L, <2mmol/L or do not feel symptoms

Refer to DAFNE program where appropriate
glycaemic control were considered. The need to include the most relevant constructs for clinical care, to identify those most in need and maximise the utility and expertise of current staff was considered. This brief comprehensive tool encompasses multiple constructs, including diabetes distress, depression and anxiety, well-being, hypoglycaemia-unawareness, fear of hypoglycaemia, social support, weight, shape and eating concerns and financial concerns. It includes three validated measures, the PAID, the K10 and the WHO-5, of which the WHO-5 and PAID are found on a national diabetes database allowing comparison between centres. When scoring the psychosocial screening tool, diabetes distress is characterised by PAID scores ≥30. A positive mental health screen is considered a K10 score ≥22 and/or WHO-5 score ≤13. Useful care is considered at an annual review with each member of the multi-disciplinarian team.

The screening tool will be implemented prior to their consultation at the routine clinic in a staged process on an annual basis. The credentialed diabetes educator will address the results of the screening tool with the young person at their clinic visit, and they can elect to engage in the patient-specific management plan.

There is a need to assess diabetes specific distress and depression concurrently, as although they are related they can be separate constructs requiring different treatment modalities.28,29 Some young adults will have general distress not related to their diabetes, which could include dysfunctional family relationships, history of abuse, loss of autonomy or bereavement, financial concerns, or lack of social support, and even early stages of disordered eating.30 Our results indicate approximately one third (27.7%) of those with disordered eating and half (47%) of those with financial concerns had PAID scores <30 and/or K10 scores <22. These findings, as well as the identification of patients positive for depression, but not diabetes distress are highlighted in the care pathway (Fig. 2) by the possibility of a mental health referral even if the PAID score is low.

Interventions to manage diabetes distress for adults with type 1 diabetes are just emerging, though few address young people specifically. Diabetes self-management education appears to reduce diabetes distress in type 1 diabetes, with the most evidence available for the Dose Adjustment For Normal Eating (DAFNE) programme, a group-based intervention.29 Allied health and diabetes nurse educators have been upskilled in motivational interviewing, motivational enhancement therapy and DAFNE principles. The service aim is to provide consistent education, and to refer as many participants as possible into the DAFNE programme. Studies have shown attendance at a DAFNE course reduces diabetes distress, severe hypoglycaemia and DKA admissions, along with small, but significant changes in HbA1c.31,32 DAFNE is cost-effective, evidenced by a 64% reduction in emergency health costs for DKA and severe hypoglycaemia.31 A service challenge is to make courses available to as many clinic attendees as possible.

We estimate 60% of attendees to our clinic require additional allied health support (diabetes educator, psychology, dietitian and/or social worker) over and above routine clinical care and education.34 The screening tool and care pathway will assist in directing those with psychosocial concerns to the appropriate healthcare professionals, improving patient care, patient satisfaction and staff satisfaction with the service. Diabetes distress scores, depression and anxiety, quality of life, HbA1c, attendance rates and occasions of service will be monitored. Those who score positively on the weight, shape control of eating questions and will be given a validated eating disorder screening tool and directed to a disordered eating management plan where needed. Social support and financial concerns will be discussed and referrals can be made to a social worker. Fear of hypoglycaemia and hypoglycaemia-unawareness will be addressed by the credentialed diabetes educators all of who have observed the DAFNE course.

As a result of the care pathway more young people will be made aware of the availability of the DAFNE course.

This screening tool and care pathway has been established for a tertiary referral diabetes clinic in a purpose-built young adult centre. Most attendees at the clinic are Caucasian (93.4%), and living in a metropolitan region (94.7%). Additionally, it is a multidisciplinary service with significant staff resources and skills, which needs to be considered if applying the model to other services. For services with less multidisciplinary resources, incorporating other allied health providers (e.g. child and adolescent mental health services, private practitioners or the medicare-funded ‘Better Access Service’), is possible. The K10 is a generic measure, used to allow comparison with other young people with and without other chronic health conditions. In the future, we plan to assess the concurrent validity of the Patient Health Questionnaire (PHQ-4) against the K10.

Similar studies to report on psychosocial profiles, screening tools and care pathways are underway for young people with other chronic conditions, such as inflammatory bowel disease, cystic fibrosis, chronic rheumatic conditions, phenylketonuria, craniofacial deformities and cancer survivors. The burden of illness will be compared across these medical conditions.

**Conclusion**

Following psychosocial screening, an abbreviated tool and associated care pathways were developed for routine
use in a young adult tertiary referral diabetes clinic. This will provide a longitudinal data source for research, to inform clinical practice and service requirements (care management needs, staffing needs) and enable screening and management protocols to be reviewed. Future research will assess the benefits of this intervention in terms of changes in access to allied health, including the DAFNE intervention, glycaemic control and short and longer-term complication rates.

Acknowledgements

We thank our colleagues for their input into developing the screening tool and care plan: Trish Bowden, Joanne Pennisi, Jane Degenaars, Carolyn Uhllmann (Queensland Diabetes and Endocrine Centre, Mater Health, Brisbane), Helen Buckle and Samantha Ferguson (Young Adult Support Centre, Mater Health), Merilyn Telay and Tamara Addley (Allied Health, Mater Health, Brisbane).

References

27 Bryden KS, Neil A, Mayou RA, Peveler RC, Fairburn CG, Dunger DB.
Heart disease in East Timor: cross-sectional analysis of 474 patients attending Timor-Leste’s first cardiology service

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1East Timor Hearts Fund, and 2St Vincent’s Health Melbourne, Melbourne, Victoria, Australia

Key words
global health, rheumatic heart disease, congenital, Australasia.

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Abstract

Background: East Timor is a developing country and is a close neighbour of Australia. The prevalence of cardiac disease is unknown.

Aims: To describe the prevalence and patterns of cardiac disease in patients attending the first cardiology service of Timor-Leste.

Methods: A cross-sectional retrospective analysis was performed of demographic and clinical data of 474 unique patients referred to outpatient cardiology clinics conducted in East Timor from 2003 to 2016.

Results: Mean age was 29.9 ± 18.5 years, with females significantly younger than males (28.8 ± 16.9 vs 32.3 ± 20.6 years). Congenital cardiac disease patients were the youngest (15.5 ± 13.9 years) and cardiomyopathy patients the oldest (46.7 ± 17.8 years).

Of patients with rheumatic heart disease, the majority had mitral stenosis (59.4%) and multi-valvular involvement (61.6%). Of note, 28.3% of patients with rheumatic heart disease presented with severe mitral stenosis. Amongst congenital heart disease patients, the most common diagnosis was atrial or ventricular septal defects (61% combined). A total of 19.2% of patients either required immediate referral for intervention or palliation for their cardiac disease. Patients referred to Australia for treatment were significantly younger (19.7 ± 11.7 years) than all other outcome groups.

Conclusion: Amongst young East Timorese, rheumatic heart disease and unrepaired congenital cardiac defects impose a significant burden. One-fifth of patients present to clinics with severe disease requiring urgent referral for surgery or palliation.

Funding: None.
Conflict of interest: None.

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Introduction

East Timor (also known as Timor-Leste) is a country of 1.2 million people and one of Australia’s closest neighbours. Located approximately 1 h north of Darwin, it is the newest country in the Asia-Pacific Region, having formally gained independence from Indonesia in 2002.1 Economically, East Timor is extremely poor, placed 133rd of the 143 countries on the World Health Organization (WHO)’s 2015 Human Development Index.2 A total of 64% of East Timorese live in poverty and 31% in severe poverty, with widespread malnutrition.3 Infant, under-five and maternal mortality occur at 30–50 times the rate of equivalent indices in Australia.2

In East Timor, there are no specialist cardiac services, interventional cardiology nor cardiac surgery. Rheumatic heart disease appears to be common, but the exact prevalence is unquantified. Congenital cardiac lesions are often fatal; survivors are typically left with varying levels of cardiac failure because of chronic pressure and volume overload.

The East Timor Hearts Fund (ETHF) has been operating since 2003 to address the East Timorese need for cardiac services and was formally recognised as an Australian charitable foundation in 2010. Australian cardiologists travel twice per year to Dili and conduct a base clinic within the premises of Bairo Pite Clinic or the Dili National Hospital. Outreach mobile clinics also travel to the rural areas of Oecusse, Bakita, Baucau and Maliana. Patients are primarily adults and adolescents as separate paediatric clinics are conducted through the Rotary Oceania Medical Aid for Children organisation. Patients are typically referred to the ETHF clinic by local doctors who have detected a cardiac murmur, irregular pulse or have already treated the patient for cardiac symptoms of angina, dyspnoea or cardiac failure.

The purpose of the ETHF is to provide local clinical consultations and echocardiography to identify East Timorese with cardiac disease. Patients who are suitable candidates for cardiac interventions are then supported by the ETHF to travel to Australia and undergo definitive cardiac intervention. The ETHF has brought almost 50 patients to Australian hospitals for a variety of interventions, including mitral balloon valvuloplasty, closure of patent ductus arteriosus, electrophysiological ablation of Wolf–Parkinson–White syndrome, repairs of septal defects and pericardiectomy for tuberculous pericarditis. All surgeries are funded by Australian donors and undertaken voluntarily by Australian doctors.

To date, there has been no formal study assessing the burden and characteristics of cardiac disease in Timor-Leste. Although a prospective school screening programme is in progress, there are currently no published data with which to anticipate likely prevalence findings or project future healthcare demands. Based on our database of almost 500 unique patients, we undertook to report for the first time the prevalence and forms of cardiac disease amongst East Timorese patients attending our cardiology clinic.

Methods

Data collection at the clinic

Since the inception of the ETHF, demographic and clinical data have been recorded for all patients attending the cardiology clinics. On presentation to the clinic, Tetum and Bahasa interpreters assist with the confirmation of name, birth date (using year only if exact birth date is not known), current age, address and contact details. Each patient is then issued with a unique identifier number, which identifies their case history through all subsequent clinic visits, hospital admissions and transfers to Australia.

In the clinic room, the patient’s history is clarified with the assistance of an interpreter, and a focused cardiovascular examination is performed. All patients then undergo a brief echocardiogram, typically taking around 10 min (Fig. 1). Echocardiograms are performed at the bedside using a portable Vivid i™ cardiovascular ultrasound machine (Vivid i machines, GE Healthcare, Buckinghamshire, UK). Echocardiographic findings are recorded on a standard proforma sheet. For patients in whom severe pathology is detected, or there is uncertainty about the diagnosis, a formal echocardiographic study is arranged.

All demographic and clinical data for each patient are entered into an Excel spreadsheet maintained on an offline laptop computer at the clinic. This ETHF database is

Figure 1 Screening echocardiography is undertaken in the East Timor Hearts Fund clinic by Dr Noel Bayley. Photo credit: Mat Lynn.
also encrypted and password-protected. Two data entry administrators manually double-enter data both on paper and electronically. At the completion of each clinic day, collected data are cross-checked between administrators to ensure accuracy. Given the infrequency of the clinics, language barriers and severity of many patients’ cardiac conditions, great emphasis is placed on accurate documentation, with clear management and follow-up plans for each patient.

Analytic methods

In this study, we examined the clinical and echocardiographic characteristics of Timorese patients presenting to the clinic for the first time and undergoing screening echocardiography. As a predefined cross-sectional analysis, we utilised the Strengthening the Reporting of Observational Studies in Epidemiology protocol in guiding study design and assessment.4 Institutional ethics approval for this data analysis was granted by St Vincent’s Hospital Melbourne (QA approval 071/16).

We utilised the ETHF database and included only first-visit data. Cardiac conditions were classed as ‘rheumatic heart disease’, ‘congenital cardiac disease’, ‘cardiomyopathy’, ‘normal’ or ‘other’. Within each classification, sub-classifications were documented to elaborate further upon presenting diagnosis. Mean age and gender distribution were calculated for overall data and also within each cardiac diagnosis group. Clinical management plans were categorised as either ‘ongoing clinical review’, ‘referral for cardiac intervention’, ‘no available treatment options’ or ‘discharged from care’.

All categorical variables are presented as percentage values. Continuous variables are presented as mean values with standard deviations. A Chi-squared test was used to test for the significance of between-group differences for categorical variables. A two-tailed t-test was used to test for the significance of between-group differences for continuous variables. One-way analysis of variance with post-hoc Tukey testing was used to test the significance of between-group differences for continuous variables when the group number was greater than two. All statistical calculations were performed using the STATA 2015 software package (STATA Corp, College Station, TX, USA).

Results

Data from 766 patient encounters were stored in the ETHF database. When first clinical encounters were only included, the sample size was reduced to 474 patients (Table 1).

Mean age overall was 29.9 ± 18.5 years, with females significantly younger than males (28.8 ± 16.9 vs 32.3 ± 20.6 years, P = 0.0495). There were large age differences between cardiac diagnosis groups, with congenital cardiac disease patients aged 15.5 ± 13.9 years, rheumatic heart disease patients aged 28.5 ± 14.8 years and cardiomyopathy patients aged 46.7 ± 17.8 years. There were no gender differences in age within the cardiac diagnosis groups.

Of patients presenting with rheumatic heart disease, the majority had mitral stenosis (59.4%) and multi-valvu lar involvement (61.6%). Of note, 28.3% of patients with rheumatic heart disease attending the cardiology clinic for the first time presented with severe mitral stenosis. A gender difference was noted amongst patients with rheumatic aortic regurgitation, with a disproportionate number being male (68.3 vs 41.2%, P = 0.004).

<table>
<thead>
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<th>Table 1 Overall statistics by cardiac diagnosis</th>
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<tr>
<td></td>
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<tr>
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<tr>
<td>Overall number</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Severe mitral stenosis</td>
</tr>
<tr>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
</tr>
<tr>
<td>Multi-valve involvement</td>
</tr>
<tr>
<td>Congenital conditions</td>
</tr>
<tr>
<td>Mean age (years)</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Normal</td>
</tr>
</tbody>
</table>

Bold values indicate statistical significance (P < 0.05).
Amongst patients presenting with congenital heart disease (Table 2), the most common diagnosis was ventricular septal defect (41.0% of patients). Other common pathologies included atrial septal defects (20.5%), and pulmonary stenosis (10.8%). Age at presentation varied by a large degree according to diagnosis, ranging from a mean of 9.0 years for pulmonary stenosis to 36.5 years for congenital abnormalities of the aortic valve.

Cardiomyopathy of both non-ischaemic and likely aetiologies was noted in 5.4% of patients referred to the clinic. Cardiomyopathy was typically severe, with left ventricular ejection fraction of 5–10% by the time of diagnosis. Patients with cardiomyopathy were amongst the oldest East Timorese reviewed at the clinic, with a mean age of 46.7 ± 17.8 years. No gender differences were identified in the cohort of patients diagnosed with cardiomyopathy.

Clinical management plans (Table 3) were documented for 466 patients (98% of group). Of 474 patients presenting for first cardiac review, 70 (14.8%) required immediate referral for intervention, and 21 (4.4%) were deemed to have no realistic treatment options. The majority (58.4%) of patients were scheduled for review appointments. Patients who were referred to Australia for surgery were significantly younger (19.7 ± 11.7 years) than all other clinical management groups (P < 0.0001). There were no significant gender differences with regards to the clinical management plan.

### Discussion

Our study is the first assessment of the burden and nature of cardiac disease in East Timor. Of patients presenting to the ETHF Cardiology Clinic, one in five will present with severe disease requiring either urgent referral for intervention or palliation at first assessment. This is in a patient group with a mean age under 30 years. It is particularly notable that one-third of patients with rheumatic heart disease present with severe mitral stenosis.

Significant gender differences were observed in the proportions and ages of patients referred to the ETHF clinic. In our study, women represented the majority of patients (60.8%) attending clinic, and particularly the majority (70.3%) of patients with rheumatic heart disease. A similarly designed retrospective study in Nigeria of patients aged 5–60 years also identified rheumatic heart disease more commonly in women, with an odds ratio of 1.7. Likewise, a school screening echocardiographic study in India identified an odds ratio of 1.84 for females presenting with rheumatic heart disease, and women were also disproportionately overrepresented in Indonesian and Ethiopian echocardiographic studies. However, paediatric screening echocardiography programmes in Malawi, Senegal, Peru and the Northern Territory of Australia have not identified significant gender differences in the burden of rheumatic heart disease. The reason for the different findings of each of these studies is not clear and may relate to the different ages of patients enrolled in each study, cultural patterns of medical referral and outreach in each country and varying use of WHO and World Heart Federation echocardiographic criteria for diagnosis of rheumatic heart disease.

On average, women were also 3.5 years younger than males at first diagnosis of cardiac disease. A contributor in some cases may be the ‘unmasking’ effects of pregnancy, with increased cardiac demand and physiological stress resulting in the earlier recognition of cardiac disease in Timorese women. Significant gender differences in age of presentation have not previously been specifically reported upon in other echocardiographic studies or systematic reviews.

Valve tropism, or the variant effects of rheumatic heart disease upon cardiac valves, has previously been reported, although the underlying pathophysiology has not been clearly elucidated. In the majority of studies conducted in Asia, and in our study also, mitral stenosis was the predominant lesion reported in rheumatic heart disease. However, screening studies in India and Africa have reported mitral regurgitation or mixed mitral valve disease as the most common valvular presentation of rheumatic heart disease. Multi-valvular involvement was common in our dataset, occurring in 61.6% of patients, while in an Indonesian echocardiographic study, multi-valvular involvement occurred in only 6.0% of patients. The elevated rate of multi-valvular disease in our cohort is most likely to relate to later presentation and diagnosis, but again, varying use of WHO versus World Heart Federation echocardiographic criteria may lead to differences in reported patterns of rheumatic heart disease.

Unrepaired congenital cardiac disease was a relatively common (17.1%) cause of presentation, with the attendant complications of abnormal volume and pressure...
Ischaemic cardiomyopathy was very infrequently observed in the ETHF clinic patients, yet WHO figures suggest that ischaemic heart disease is the third most common cause of death in East Timor. Given the absence of coronary angiography or cardiac surgery in East Timor, the most likely interpretation of these dissonant figures is that acute coronary syndromes are, by necessity, managed conservatively and, consequently, are often fatal events. The ‘survivorship group’ of patients with ischaemic cardiomyopathy who survive to attend outpatient echocardiography is therefore understandably low.

Clinical outcomes and management were well-documented and differed according to age, with younger patients being significantly more likely to be referred to tertiary cardiac centres in Indonesia or Singapore. This expatriation of cardiac care amongst the wealthier citizens of East Timor is likely to create under-documentation of the true burden of conditions, such as stable ischaemic heart disease. Indeed, as discussed earlier, the rate of ischaemic cardiomyopathy captured in our dataset appeared to be very low.

There is also a geographic bias in our dataset in that the ETHF clinic is predominantly attended by poorer Timorese citizens. Cardiac disease occurring in higher socioeconomic classes (such as the political class and their extended families, the business class and military families) is presumed to be markedly underrepresented as these citizens typically would not attend local volunteer clinics but would fly out to tertiary cardiac centres in Indonesia or Singapore. This expatriation of cardiac care amongst the wealthier citizens of East Timor is likely to create under-documentation of the true burden of conditions, such as stable ischaemic heart disease. Indeed, as discussed earlier, the rate of ischaemic cardiomyopathy captured in our dataset appeared to be very low.

Finally, data collection in a foreign language in a developing country also poses unique challenges. However, as detailed earlier, great efforts have been made over many years to ensure data integrity, primarily to ensure appropriate clinical follow up in the first instance.

Given that previously no clinical data have been reported for the prevalence of rheumatic or congenital heart disease in East Timor, we believe that this ETHF dataset is clinically novel and provides a useful foundation for future project and resource development.

**Conclusion**

This is the first data set to report on the prevalence and nature of cardiac disease in Timor-Leste. Rheumatic
heart disease is common and occurs more frequently in females. Almost one-third of patients present with severe mitral stenosis at diagnosis. One-fifth of patients present to the clinic with severe disease requiring urgent referral for surgery or palliation, this in a patient group with a mean age lower than 30 years. Further studies into the prevalence and patterns of cardiac disease in East Timor will assist with the development of local cardiac resources.

Acknowledgement

We acknowledge Ms Julie Kean (East Timor Hearts Fund), who initiated and maintained the ETHF database.

References

Exploratory study into the unmet supportive needs of people diagnosed with cirrhosis in Queensland, Australia

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Key words
cirrhosis, supportive care, support services, health professionals, unmet needs.

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Abstract
Background: Many patients with cirrhosis follow complex medication and dietary regimens, and those with decompensated cirrhosis suffer debilitating complications. These factors impact activities of daily living and quality of life.
Aims: To explore the concerns and challenges of people with cirrhosis and their use of support services and to also describe health professionals’ (HP) perspectives of patients’ concerns.
Methods: This is a cross-sectional study at a tertiary liver clinic involving 50 patients and 54 HP. Data were collected using structured questionnaires. The study includes patients’ report of their challenges/problems now that they have cirrhosis (patient-volunteered concerns) and HP report of patients’ concerns. Both also ranked a list of 10 potential concerns.
Results: Patients were, on average, 58 years old (SD = 10.2), mostly male (78%), Caucasian (86%) and with compensated cirrhosis (60%). The patients’ most common volunteered concerns related to managing symptoms, emotional issues and disease. Most ranked ‘developing liver cancer’ (79%), ‘losing ability to do daily tasks for yourself’ (76%), ‘fear of dying’ (64%) and ‘fear of the unknown’ (64%) as priority concerns. Regarding the use of support services, 24% of patients had accessed a dietician, 20% a pharmacist and 18% a psychologist. From the HP perspective, the patients’ most significant challenges related to managing disease (65%) and symptoms (48%), access to healthcare (56%) and information/knowledge (48%).
Conclusions: Our findings demonstrate that cirrhosis (its symptoms, complications and treatment) is associated with significant concerns for patients. The discrepancies between the views of HP and patients suggest that we may not be measuring or addressing patients’ needs appropriately.

Introduction
Chronic liver disease (CLD) is a major global cause of morbidity and mortality. It affects approximately 300 million people in China,1 29 million in the European Union2 and 8 million in Australia.3 Regardless of aetiology, morbidity and mortality from CLD principally occurs among cirrhotic patients. Most follow complex medication regimens and dietary restrictions,4 and those with decompensated cirrhosis suffer debilitating complications (e.g. extreme fatigue, ascites, hepatic encephalopathy). These factors impact activities of daily living and quality of life, meaning that these patients likely have high levels of supportive care needs.

A recent review of 26 papers,5 specifically concerning patients with hepatitis C, reported experiences and concerns of people diagnosed with CLD worldwide. Five key domains of supportive care needs were identified in this review: informational or educational, practical, physical, patient care and support and psychological. A total of

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14 studies using quantitative methodology and 12 qualitative studies highlighted the unmet needs of CLD patients and the paucity of data. However, there is very little information on patients with cirrhosis (three papers only), who are the most likely to have high supportive care needs.

The current study is a novel exploratory assessment of the concerns and challenges of people diagnosed with cirrhosis attending a tertiary hospital hepatology clinic in Queensland, Australia. We describe the principal concerns or unmet supportive care needs of people diagnosed with cirrhosis and their use of support services. We also describe the perspective of health professionals (HP), assessing their perceptions of patients’ concerns and requirement for support services. This is important in order to determine where inconsistencies exist between patients’ needs and HP perceptions.

Methods
A cross-sectional study was conducted at the Princess Alexandra Hospital, Brisbane, a tertiary healthcare facility with specialist gastroenterology/hepatology services and the referral centre for the state-wide liver transplant service. Two groups of participants were included: patients diagnosed with cirrhosis and HP (August 2014 to July 2015).

Current adult patients of the hepatology clinic diagnosed with cirrhosis by a healthcare provider were eligible. Patients were excluded if their treating clinician considered them to have a cognitive or physical impairment that could interfere with participation (e.g. dementia, current encephalopathy) or if they were unable to communicate in English. A study nurse (LH) and a hepatologist (EP) assessed patients’ eligibility, obtained written approval and collected data using a structured interview that included a series of closed- and open-ended questions. The face-to-face interviews were conducted in English and included socio-demographic characteristics, questions about challenges/concerns in the context of cirrhosis and a question about the use (currently or previously) of supportive care services. Patients were asked one open-ended question: ‘What is the most significant challenge or problem for you now that you have liver disease?’ (referred to here as the ‘patient-volunteered concern’). Similar to Minuk et al.⁵ and Balfour et al.,⁶ patients were then provided with a list of 10 potential concerns (informed by a systematic literature review on the supportive care needs in CLD⁷) and asked to prioritise 5 of the most important to them (ranked from 1 = most important to 5 = least important) without assistance from the interviewer.⁸ Clinical information was extracted from medical records.

A convenience sample of HP working in the hepatology and transplant wards, day surgery and treatment unit and gastroenterology outpatient department were invited to participate. Data were collected using a self-completed questionnaire of closed- and open-ended questions (consistent with those addressed to patients) as well as questions about occupation and experience. Similar to the patients’ questionnaire, HP were asked: ‘In your opinion, what are the most significant challenges or problems for patients with cirrhosis?’ (referred to here as the ‘HP-volunteered concern’) and were also asked to rank the same list of potential patient concerns. They were then asked ‘What support services/resources would be most helpful for patients with cirrhosis and their families?’ (open-ended question) and which of a list of 10 support services ‘ideally would be free and easily accessed by patients with cirrhosis and/or their families’ (HP were asked to select all services that they felt patients may benefit from).

Data analysis was conducted using SPSS Inc version 22.0 (StatCorp LP; 2013, College Station, TX, USA). Participants’ characteristics were analysed for mean and standard deviation (data normally distributed) and/or proportions. Chi-square tests were used to compare proportions (Fisher’s exact test was used when cell counts were less than 5). All P values were two-sided, and statistical significance was set at alpha = 0.05. Similar to Minuk et al.,⁵ mean scores (and standard deviation) were calculated for each ranked concern. Responses to open-ended questions were examined utilising standard qualitative procedures that entail the identification of themes within the responses.⁵ Microsoft Excel (Microsoft Office Professional Plus 2010) was used to classify answers into meaningful categories.

Informed consent was obtained from participants, and the protocol was approved by the Metro South Hospital and Health Service and the University of Queensland Human Research Ethics Committees (HREC/99/QPAH/076; UQ2003000092).

Results
Patient population
A total of 53 consecutive patients with cirrhosis attending the hepatology clinic was invited to participate, and 50 (94%) were interviewed. Participants were aged 39–90 years (mean 58 years, SD = 10.2), with the majority being male (n = 39, 78%), Caucasian (n = 43, 86%), Australian born (n = 36, 72%), English speakers at home (n = 48, 96%) and confident with written English (n = 48, 96%). Over half had a high school education level or higher (n = 26, 52%); most were currently unemployed (n = 34, 68%) and lived with a partner,
child or a friend \( (n = 37, 74\%) \), while 13 patients \( (26\%) \) lived alone.

The most common aetiologies of cirrhosis were the hepatitis C virus \( (n = 26, 52\%) \), fatty liver disease \( (n = 11, 22\%) \) and alcohol excess \( (n = 9, 18\%) \), while seven \( (14\%) \) patients had alcohol as a co-factor. A total of 20 patients \( (40\%) \) had a history of oesophageal varices, 30\% \( (n = 15) \) at least one episode of ascites, 12\% \( (n = 6) \) at least one episode of jaundice, 6\% \( (n = 3) \) at least one episode of hepatic encephalopathy, and four patients also had hepatocellular carcinoma; 60\% \( (n = 30) \) of participants had compensated cirrhosis.

**Patients’ concerns and use of support services**

The most common patient-volunteered concerns included management of symptoms (e.g. fatigue/tiredness, decreased mobility, ascites, lack of energy; 34\%), emotional issues (e.g. scared, stressed, lack of motivation, depression, confused; 28\%), disease management (e.g. weight control, exercise, side-effects of treatment; 20\%) and stopping alcohol/substance abuse (12\%) (Fig. 1). Eight (16\%) patients did not volunteer any concern.

Of the 50 patients interviewed, data about ranking concerns were not available for 17 participants (24\%): 9 answered questions inappropriately, 2 could not read, 2 had trouble understanding the questions, 3 refused to answer these questions and 1 patient expressed no concerns. The most common prioritised concerns were: ‘developing liver cancer’ (79\%) followed by ‘losing ability to do daily tasks for yourself’ (76\%), ‘fear of dying’ (64\%) and ‘fear of the unknown – what the future holds’ (64\%; Table 1). When the results were analysed by mean scores, the highest priority scores were for ‘developing cancer’ (2.5, SD = 1.3) followed by ‘fear of dying’ (2.6, SD = 1.6).

Most participants (78\%) felt confident about controlling their symptoms, but 56\% acknowledged worrying about their health, particularly those with decompensated cirrhosis (75 vs 43\% with compensated cirrhosis, \( P = 0.027 \)). Most patients identified someone upon whom they could depend for assistance if really needed (90\% had someone they can talk to about important decisions in life), and 86\% saw a general practitioner regularly. A total of 13 patients (26\%) had an enduring power of attorney, but only 1 (2\%) had an advance health directive in place. While nine patients (18\%) did not have an advance health directive, a staggering 80\% \( (n = 40) \) did not know what that was. Nearly one-third of patients (30\%) needed to take time off work for treatment/review of their disease (all males, \( P = 0.021 \), and 69\% had to travel over 30 min to receive treatment. There were no other statistically significant differences in the impact of CLD by gender, age group or compensated/decompensated status (data not shown).

Regarding support services, participants had accessed a dietician (24\%), pharmacist (20\%), psychologist (18\%), spiritual support (16\%), psychiatrist (16\%), complementary medicine practitioner (10\%), home help (10\%), mental health team (8\%) and/or social worker (6\%) for assistance. No participants reported accessing palliative care services. Of five patients who volunteered a concern about eating/losing weight, only one (20\%) had accessed a dietician. Of 21 patients ranking ‘fear of dying’ as one

![Figure 1](https://via.placeholder.com/150)
Table 1 Prioritised concerns of 33 patients and 50 health professionals who answered the questions and ranked concern items

<table>
<thead>
<tr>
<th>Concern item</th>
<th>Number of participants (%) ranking this item in the top five</th>
<th>Number of participants (%) ranking this item in the top five</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing liver cancer</td>
<td>26 (79)</td>
<td>19 (38)</td>
<td>2.5 (1.3)</td>
<td>3.2 (1.3)</td>
<td>3.0 (2)</td>
<td>3.0 (2)</td>
</tr>
<tr>
<td>Losing ability to do daily tasks for yourself</td>
<td>25 (76)</td>
<td>36 (72)</td>
<td>2.9 (1.2)</td>
<td>2.9 (1.4)</td>
<td>3.0 (2)</td>
<td>3.0 (2)</td>
</tr>
<tr>
<td>Fear of dying – shortened life expectancy</td>
<td>21 (64)</td>
<td>35 (70)</td>
<td>2.6 (1.6)</td>
<td>2.0 (1.3)</td>
<td>1.0 (2)</td>
<td>1.0 (2)</td>
</tr>
<tr>
<td>Fear of the unknown – what the future holds</td>
<td>21 (64)</td>
<td>34 (68)</td>
<td>3.6 (1.4)</td>
<td>3.5 (1.1)</td>
<td>3.5 (2)</td>
<td>3.5 (2)</td>
</tr>
<tr>
<td>Lack of treatments for cirrhosis</td>
<td>18 (55)</td>
<td>28 (56)</td>
<td>2.8 (1.5)</td>
<td>2.8 (1.5)</td>
<td>3.0 (3)</td>
<td>3.0 (3)</td>
</tr>
<tr>
<td>Costs and money</td>
<td>12 (36)</td>
<td>28 (56)</td>
<td>3.2 (1.6)</td>
<td>3.2 (1.3)</td>
<td>3.5 (2)</td>
<td>3.5 (2)</td>
</tr>
<tr>
<td>Infecting family or others</td>
<td>11 (33)</td>
<td>8 (16)</td>
<td>3.4 (1.5)</td>
<td>3.5 (2)</td>
<td>3.5 (3)</td>
<td>3.5 (3)</td>
</tr>
<tr>
<td>Side-effects of treatment</td>
<td>11 (33)</td>
<td>14 (28)</td>
<td>3.8 (1.3)</td>
<td>3.6 (1.4)</td>
<td>4.0 (2)</td>
<td>4.0 (2)</td>
</tr>
<tr>
<td>Frequent hospital visits–admissions</td>
<td>10 (30)</td>
<td>38 (76)</td>
<td>3.4 (1.5)</td>
<td>2.6 (1.4)</td>
<td>2.0 (3)</td>
<td>2.0 (3)</td>
</tr>
<tr>
<td>Social stigma of having liver cirrhosis</td>
<td>10 (30)</td>
<td>15 (30)</td>
<td>2.8 (1.1)</td>
<td>3.7 (1.1)</td>
<td>4.0 (2)</td>
<td>4.0 (2)</td>
</tr>
</tbody>
</table>

† Average score for participants who ranked each item between 1 and 5. IQR, interquartile range.

of their top five concerns, 7 (33%) had accessed a psychologist. There were no statistically significant differences in accessing services by gender, age group or compensated/decompensated status (data not shown).

Health professionals

Of the 59 HP invited to participate, 54 (92%) were interviewed (5 refused/failed to return the survey). Participants were mostly female (n = 40, 74%), aged 25–44 years (n = 29, 54% with 9% younger and 37% older), representing a range of occupations, including 15 doctors (28%), 30 registered nurses (56%), 2 administrative support persons (4%), 2 dieticians (4%), 1 social worker (2%) and 4 pharmacists (7%). Most (63%) had worked in their occupations for at least 5 years: 4 (7%) for <1 year, 16 (30%) for 1–5 years, 12 (22%) for 5–10 years and 22 (41%) for 10+ years. While all HP had worked with patients with cirrhosis, a wide range of experience was reported, with 8 (15%) having worked in the field for <1 year, 22 (41%) between 1 and 5 years and 24 (44%) for 5+ years; most had either daily (n = 34, 63%) or weekly (n = 28, 52%) contact with patients with cirrhosis.

HP’s opinion about patients’ concerns and desirable support services

According to HP, the most significant challenges or problems faced by patients included disease management (e.g. diet and fluid restrictions, medication burden, medication adherence, compliance with treatment, lifestyle changes; 65%), access to healthcare (e.g. frequent medical appointments, loss to follow-up, treatment burden, lack of resources, access to palliative care; 56%), management of symptoms (e.g. tiredness, ascites, fluid imbalance, complications; 48%) and information/knowledge (41%) (Fig. 1).

Data on ranking concerns were available for 50 out of 54 participants (4 participants (7%) did not answer the questions appropriately). The most common HP-prioritised concerns were: ‘frequent hospital visits–admissions’ (76%), ‘losing ability to do daily tasks for yourself’ (72%), ‘fear of dying – shortened life expectancy’ (70%) and ‘fear of the unknown – what the future holds’ (68%) (Table 1). When the results were analysed by mean scores, the highest priority scores were for ‘fear of dying – shortened life expectancy’ (2.0, SD = 1.3) followed by ‘frequent hospital visits–admissions’ (2.6, SD = 1.4) and ‘losing ability to do daily tasks for yourself’ (2.9, SD = 1.4).

Support groups or services (e.g. social worker, support groups, spiritual support) were volunteered by the majority (57%, 27 out of 47 HPs who answered this question appropriately) as services or resources that would be most helpful for patients and their families. Health services (e.g. phone consults, family doctor, cirrhosis nurse coordinator, dietician, mental health service, palliative care, pharmacist in outpatient clinic, community follow-up/liaison officer) were also popular (45%), followed by information services (e.g. information pamphlets, educational services, low salt recipes; 21%), financial support (e.g. transport, Centrelink disability support; 9%) and home services (e.g. home care, support for day activities; 6%).

From a list of 10 proposed support services, most supported each service as being ‘ideally free and easily accessed by patients and their families’ (Table 2). In particular, most (over 90%) felt that patients with cirrhosis
Table 2 Frequency of health professionals selecting services that they felt patients with cirrhosis and their family may benefit from

<table>
<thead>
<tr>
<th>List of service</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol/Other drug abstinence support</td>
<td>51 (94)</td>
</tr>
<tr>
<td>Frequent hospital visits/admissions – Nursing Care</td>
<td>50 (93)</td>
</tr>
<tr>
<td>Palliative Care/Health Planning – Advance Health Directive – how to discuss these issues with my family</td>
<td>49 (91)</td>
</tr>
<tr>
<td>Losing ability to do daily tasks for yourself – who can help you stay in your home for as long as possible</td>
<td>46 (85)</td>
</tr>
<tr>
<td>How to stay healthy and happy with cirrhosis booklet (diet, exercise, natural history, when to seek assistance)</td>
<td>45 (83)</td>
</tr>
<tr>
<td>Financial planning assistance (Centrelink support/disability car sticker)</td>
<td>45 (83)</td>
</tr>
<tr>
<td>Cirrhosis peer support ( Individual or Group Monthly Meeting)</td>
<td>44 (82)</td>
</tr>
<tr>
<td>Developing liver cancer – what do I do now? Nursing</td>
<td>38 (70)</td>
</tr>
<tr>
<td>Education and Care Coordination</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A and B vaccination at clinic – patient and family members if appropriate</td>
<td>37 (69)</td>
</tr>
<tr>
<td>Spiritual support – in a form appropriate to the individual patient</td>
<td>30 (56)</td>
</tr>
</tbody>
</table>

†Government-funded financial support

Discussion

This study aimed to explore the diversity of concerns that potentially impact the quality of life of patients with cirrhosis. It not only assessed patients’ concerns but also surveyed HP in an attempt to determine where inconsistencies exist between patients’ needs and HP’s perceptions. Our findings demonstrate that cirrhosis – its symptoms, complications and even its treatment – is associated with significant concerns that can impact patient quality of life. The recurring messages relayed by both patients and HP are that cirrhotic patients need support with the management of cirrhosis and its symptoms, emotional issues and abstinence from alcohol and/or substance abuse. With a few exceptions, patients’ concerns are consistent regardless of gender, age group or severity of cirrhosis. Compared with the patients’ interviews, generally, HP were more forthcoming in volunteering patients’ concerns and also included challenges related to access to and coordination of healthcare, information and knowledge about their disease and practical support in general (e.g. financial issues, activities of daily living and support services).

Patients and HP also differed with respect to the prioritisation of concerns. Developing liver cancer was the greatest concern for patients, whereas only 38% of HP prioritised this complication. Most HP thought that patients were most concerned with frequent hospital visits/admissions, although less than one-third of patients prioritised this issue. A disparity in the knowledge of cirrhosis and the incidence of complications as well as differing perspectives of healthcare in the tertiary hospital setting may account for these disagreements. Nevertheless, the data do suggest a disconnect between perceived and actual priorities for patients with cirrhosis, which may impact the success of treatment.

A recent review of published literature on unmet needs of people with CLD included only a small number of studies conducted in Australia, which were restricted to people diagnosed with hepatitis C (one quantitative and five qualitative studies). Concerns raised by patients included in these studies fell into the informational/educational, patient care and support, practical, physical and psychological domains. Some of the issues raised by participants included in the current study mirrored findings from these studies (e.g. symptoms, financial issues, fears of a threatened future, emotional issues, disease management). Of the 26 studies included in the review, 15 reported unmet needs or concerns in the ‘informational/educational’ domain; a perceived lack of information about disease or disease management were concerns reported in 11 studies (two conducted in Australia), while patients from 2 other studies reported receiving good support with information and/or education. Findings from one Australian study elicited differences according to gender, with men reporting a lesser impact of their illness and reduced need for social support or information about self-care, while women conversely expressed a desire for social support and health information to manage their disease better. The high proportion of men included in the current study may explain why increased information/knowledge was not volunteered as a concern by a single study participant.

Many challenges exist for caring for people diagnosed with cirrhosis. Optimal patient management requires a coordinated multidisciplinary approach that includes lifestyle modifications, such as weight loss, physical exercise and cognitive behavioural therapy as well as coordination of care and communication between specialists. The data strongly suggest that the use of relevant multidisciplinary support services is poor, with relatively few patients accessing resources despite enthusiasm from HP about the use of a wide range of support services. Patient-related factors (e.g. low patient motivation and adherence, harmful alcohol consumption and substance abuse, comorbid mental illness and logistical factors, such as travel to appointments) coupled with resource-limited access to services mean that many patients likely...
receive suboptimal care. The ability to predict accurately needs and optimise access to ancillary services to enhance patient care remains a challenge for all healthcare systems in the management of chronic disease.

This study also explored patient use of support services. A concerning finding was the relatively low proportion of patients who reported contact with support services in general. For example, only a few patients had accessed a psychologist despite emotional issues being the third most common patient-volunteered concern. Decompensated cirrhosis is a rapidly progressive disease marked by serious complications and median survival times of less than 2 years.29 Despite the fact that over one-third of the patients had decompensated cirrhosis, none had accessed palliative care services.

Effective chronic disease management requires that patients have the knowledge and skills to contribute to the self-management of their health.30,31 A range of self-management support initiatives is available from healthcare and community services to enhance patients’ ability to care for their chronic condition. Some examples of initiatives include: (i) chronic disease self-management education programmes; (ii) financial incentives for HP to provide self-management support in the form of care plans and multidisciplinary team support (e.g. government-subsidised allied health interventions); and (iii) consumer support groups. However, our findings show that, while the majority of HP felt that every proposed support service should be freely available and accessible to patients, only a minority of patients actually accessed support services. This suggests that these resources are not easily/freely accessible, that physicians or patients are unaware of the availability of these resources/services or that physicians or patients do not use support services when required. An indication that poor uptake may be the explanation is that very few patients had formal arrangements in place for medical emergencies (e.g. enduring power of attorney, advance health directive) despite the severity of their liver disease.

Study strengths include the excellent response rates from both patient and HP, the use of patients’ medical records to confirm clinical data and face-to-face patient interviews to overcome literacy concerns and patient understanding of questions. The drawback of using face-to-face interviews is that it may promote social-desirability bias, where patients answer questions in a certain way or feel inhibited in the presence of an interviewer, thereby inaccurately or incompletely disclosing their true needs. This was a small single-centre study; patients had to be able to understand English, and those with hepatic encephalopathy considered to have cognitive impairment were not interviewed. Therefore, our findings may not be truly representative of the wider population with decompensated cirrhosis. Nevertheless, this is an important exploratory study of the needs and concerns of English-speaking patients in a tertiary hospital specialist hepatology clinic.

Conclusions

This study is the first to provide insights into the many concerns and challenges of people diagnosed with cirrhosis in Australia and their use of support services. Our data suggest that cirrhosis patients not only worry about health concerns but also about the impact of their disease on social functioning and interaction. These are perhaps concerns that existing medically focused health systems are poorly equipped to address. In particular, patients with decompensated cirrhosis29 have poor prognosis, intensive symptom burden and emotional issues and therefore would greatly benefit from improved collaboration between palliative care clinicians and hepatologists32 as well as the support from healthcare and community support services.30

The discrepancies between HP and patients’ views suggest that we may not be measuring and/or addressing patients’ needs appropriately. With the increasing prevalence of cirrhosis and its mortality and morbidity, further research into the supportive care needs of this patient group and how successfully their needs are met through the use of available support services is essential to inform service development, particularly around multidisciplinary care. A supportive care needs assessment tool, specifically developed for this patient group, could be used to promote patient-centred clinical practice and provide researchers with a better understanding of patients’ supportive care needs. Better data and utilisation of a needs assessment instrument by care providers may help to enhance patient-specific service delivery and facilitate a more structured approach to ensure improved efficacy and better outcomes. Furthermore, education to patients and their carers (e.g. about cirrhosis, self-care tasks, support services available) and to HP (e.g. about support services available, the importance of multidisciplinary care and the role of palliative care) may have an important role in improving support to this vulnerable group.

Acknowledgement

We thank Mr Felipe Bortoleto (Population Health, QIMR Berghofer Medical Research Institute) for technical support.
References


Venous thromboembolism management practices and knowledge of guidelines: a survey of Australian haematologists and respiratory physicians

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Key words
venous thromboembolism, physicians, uncertainty, surveys and questionnaires, Australia.

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Abstract

Background: Current international clinical practice guidelines do not adequately address all clinical scenarios in the management of venous thromboembolism (VTE), and no comprehensive Australian guidelines exist.

Aims: To identify areas of uncertainty in VTE management and whether self-reported practice is consistent with guidelines.

Methods: We conducted an Australian cross-sectional online survey consisting of 53 questions to investigate doctors’ VTE management practices. The survey was distributed to consultant and trainee/registrar haematologists and respiratory physicians with the aid of participating medical societies.

Results: A total of 71 haematologists and 110 respiratory physicians responded to the survey. The majority of survey respondents were 31–50-years old and worked in teaching hospitals and in the acute care setting. Under-treatment was reported for high-risk pulmonary embolism (PE) and duration of anticoagulation for first-episode unprovoked PE (32 and 83% respectively). Over-treatment was reported in areas of thrombolysis for intermediate-risk PE (16%) and duration of anticoagulation for first-episode provoked PE (41%). Uncertainty and variations in doctors’ management approaches were also found.

Conclusion: This survey demonstrated significant over-treatment, under-treatment and variability in the practice of VTE management. The findings highlight the need for the development and implementation of national guidelines for the management of VTE in Australia.

Introduction

Venous thromboembolism (VTE) is a leading cause of preventable mortality in Australia. In 2008, there were 14 716 reported cases nationally, costing the medical system an estimated $1.72 billion as well as creating a significant economic burden through loss to the workforce.1

Despite the availability of multiple management guidelines, there are still significant areas of uncertainty in management.2 This is largely because of the variable prognoses of individuals with VTE and gaps in the evidence base for several important clinical scenarios. In particular, significant doubt remains regarding the optimal treatment of intermediate-risk pulmonary embolism (PE). The major institutions to publish guidelines on the management of VTE are the National Institute for Health and Care Excellence (NICE), the European Society of Cardiology (ESC) and the American College of Chest Physicians (ACCP), who have most recently published guidelines in 2012, 2014 and 2016 respectively.3–5 These guidelines are extensive; however, there is variation in their coverage and recommendations in part because of recent changes in the evidence base. The lack of a comprehensive Australian guideline creates significant uncertainty for treating clinicians, leading to discrepancies in national standards of practice. Variation in practice has been observed in prior studies, although none of the studies addresses all areas of management, and there is limited information regarding Australian practice.6–11

This study aimed to identify the extent to which self-reported VTE management practices of Australian
haematologists and respiratory physicians are consistent with currently available international guidelines. The outcomes of this study will aid the development of national clinical guidelines for the investigation and management of VTE. In addition, by identifying gaps in knowledge, the study highlights important areas for training and education.

**Methods**

**Study design and ethics**

We conducted a cross-sectional survey of haematologists and respiratory physicians currently working within Australia (Appendix S1). Both consultants and registrars/trainees were eligible to participate. The study was approved by the Melbourne Health Human Research Ethics Committee (Project number QA2015182).

**Survey development**

A draft survey was developed after an extensive literature review and review of current clinical practice guidelines. The draft survey was reviewed by 10 physicians (respiratory physicians, general physicians and haematologists) at the Royal Melbourne Hospital and Peter McCullum Cancer Centre who provided expert advice on question content and survey design. An online version of the survey was developed using Survey Monkey (www.surveymonkey.com) and was accessible through a web link. It consisted of 53 questions and took 10 min to complete.

**Survey procedure**

An email containing the link to the survey was sent to members of The Australasian Society of Thrombosis and Haemostasis, The Haematology Society of Australia and New Zealand (HSANZ) and The Thoracic Society of Australia and New Zealand (TSANZ). After an initial poor response rate, reminder emails were sent on at least one further occasion. Surveys were also distributed at TSANZ and HSANZ scientific meetings.

**Statistical analysis**

Statistical analysis was conducted using STATA IC 14.1 (StataCorp, College Station, TX, USA). Denominators for percentage calculations were adjusted to account for missing data. Chi-squared analysis was used to identify differences in survey responses between haematologists and respiratory physicians. Multivariate logistic regression was used to determine which demographic- or physician-specific factors were related to physician responses. All relevant clinical and demographic factors for which data were collected were included in the analysis, including specialty, gender, years of clinical experience, metropolitan or regional practice, private hospital workplace and reported use of guidelines. $P < 0.05$ was considered statistically significant.

**Results**

**Participation and demographics**

Of an estimated 505 haematologists and 630 respiratory physicians registered in Australia in December 2015,12 71 and 110, respectively, responded to the survey. Respondents who did not complete the survey beyond the demographic section were excluded, providing a response rate of 13% for haematologists and 16% for respiratory physicians. This is a conservative estimate based on the number of doctors registered with the Australian Health Practitioners Regulation Agency in 2016 rather than the number who are members of the societies who distributed the survey.

A total of 66% percent of respondents was 31–50-years old; the median number of years spent working in their speciality was 9 (interquartile range (IQR) (4, 19)), and over 84% worked in teaching hospitals and in the acute care setting (Table 1). The responses to survey questions are summarised in the following text, and Table 2 includes a breakdown by specialist type for all responses, which differed significantly between respiratory physicians and haematologists.

Multivariate logistic regression was used to identify physician-specific factors associated with specific management practices. All statistically significant results are presented in Table 3.

**Knowledge and use of guidelines**

Doctors were more familiar with the Australian Therapeutic Guidelines (ATG)13 and ACCP’s 2012 and 20165 guidelines (47, 44 and 54% respectively) than the ESC4 and NICE3 guidelines (21% and 27% respectively). A total of 5% of doctors was not familiar with any of these guidelines.

A total of 77% of doctors agreed that they usually base clinical decisions on one or more of these guidelines.

**Initial assessment of PE**

The vast majority of doctors (96%) were familiar with the Wells score for assessing the probability of having a
VTE; however, 38% said they would rarely or never calculate and record it. A total of 61% of doctors was familiar with the Pulmonary Embolism Severity Index (PESI). Only 25% regularly use the PESI/simplified PESI (sPESI), whereas most doctors regularly use cardiac biomarkers (60%) and/or imaginga (74%).

### Managing low-risk PE

A total of 56% of respondents usually admit a patient with low-risk PE for 1–2 days (where social circumstances and comorbidities permit early discharge). Only 4% usually admit for 3–5 days, and 40% would treat at home or discharge within 24 h.

### Table 1  Demographic data by specialty area of practice

<table>
<thead>
<tr>
<th></th>
<th>Respiratory physicians (%) n = 99</th>
<th>Haematologists (%) n = 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male 63.6 36.4 0</td>
<td>Female 55.4 43.1 1.5</td>
</tr>
<tr>
<td></td>
<td>Declined to answer 0 0 0</td>
<td>Declined to answer 0 0 0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20–40 52.5 52.3</td>
<td>41–50 27.3 23.1</td>
</tr>
<tr>
<td></td>
<td>51–60 14.1 18.5</td>
<td>61+ 6.1 6.2</td>
</tr>
<tr>
<td>Position</td>
<td>Consultant 73.7 69.2</td>
<td>Registrar/trainee 26.3 30.8</td>
</tr>
<tr>
<td></td>
<td>Acute hospital inpatient care 93.9 84.6</td>
<td>Acute hospital consultative/liaison 42.4 58.5</td>
</tr>
<tr>
<td></td>
<td>Community care 4.0 4.6</td>
<td>Outpatient 59.6 66.2</td>
</tr>
<tr>
<td></td>
<td>Private 35.4 32.3</td>
<td>Laboratory 0 6.2</td>
</tr>
<tr>
<td>Region</td>
<td>Metropolitan 93.9 84.6</td>
<td>Regional 6.1 12.3</td>
</tr>
<tr>
<td></td>
<td>Metro and regional 0 3.1</td>
<td>Hospital type</td>
</tr>
<tr>
<td></td>
<td>Teaching hospital 90.9 89.1</td>
<td>District general hospital 2.0 0</td>
</tr>
<tr>
<td></td>
<td>Private hospital 7.1 6.3</td>
<td>Community care 0 1.6</td>
</tr>
<tr>
<td></td>
<td>Laboratory 0 3.1</td>
<td>Years worked in specialty area</td>
</tr>
<tr>
<td></td>
<td>Median years [q1, q3] 9 (4, 16)</td>
<td>10 (4, 20)</td>
</tr>
</tbody>
</table>

n, sample size; q1, first quartile; q3, third quartile.

Managing high-risk PE

The majority of doctors surveyed would recommend thrombolysis for patients with high-risk PE without contraindications to thrombolysis (68%). However, 18% indicated they would rarely or never recommend thrombolysis, and 14% indicated they would only recommend thrombolysis sometimes. Using thrombolysis never or rarely was almost four times more likely amongst haematologists, six times more likely amongst doctors in private hospitals and showed a slight association with increasing years of clinical experience (Table 3).

Managing intermediate-risk PE

Recommendations for thrombolysis

The majority of doctors (84%) do not recommend the use of thrombolysis for patients with intermediate-risk PE in those without contraindications to thrombolysis. More doctors would frequently or always recommend thrombolysis for patients with elevated troponin and right ventricular dysfunction (RVD) on echocardiography (16%) than for patients with elevated troponin and RVD dysfunction on CTPA (7%). A total of 6% of doctors said they would sometimes recommend thrombolysis for patients with elevated troponin and no evidence of RVD on CTPA or echocardiography (Fig. 1).

A total of 90% of respondents reported discussing the risks and benefits of thrombolysis with their patients. However, 22% of them stated that patient preferences do not influence their decision to use thrombolysis much or at all for intermediate-risk PE.

Only 8% of doctors surveyed said they had used half-dose thrombolysis in this patient group.

Recommendations for cardiac monitoring

A total of 91% of doctors would recommend cardiac monitoring for patients with both elevated serum troponin and features of RVD on CTPA or echocardiography; 62% recommend monitoring for patients with features of RVD on CTPA or echocardiogram but without elevated troponin, while 49% recommend monitoring for

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*Computed tomography pulmonary angiogram or echocardiography.
patients with an elevated troponin but without features of RVD.

Screening for thrombophilia and malignancy

For patients with a first-episode unprovoked PE, 88% of doctors would frequently or always recommend patients be up-to-date with national screening tests. A total of 54% would recommend a thrombophilia screen; however, only 17% recommend a computed tomography (CT) chest/abdomen/pelvis or CT abdomen/pelvis to screen for occult malignancy in patients over 40 years of age.

Follow up of PE

A total of 35% of respondents routinely order a VQ scan before cessation of anticoagulation for unprovoked PE, whereas 5% would routinely order a CT; 17% routinely order either.

A total of 16% of doctors routinely use echocardiogram during follow up of individuals with unprovoked PE; 51% use echocardiography during the follow up of patients who had features of RVD and/or pulmonary hypertension detected at the time of initial diagnosis, and 45% use it for those with persisting symptoms (multiple answers were possible for this question).

Choice of anticoagulant

Assuming there are no contraindications, 76% of doctors prefer to prescribe new oral anticoagulants over vitamin K antagonists for patients with PE without cancer.

Long-term management of VTE in patients without transient risk factors

Only 40% of doctors stated they would recommend aspirin for patients ceasing anticoagulation after an episode of unprovoked PE. Only 18% of doctors said they frequently or always use follow-up d-dimer tests to guide the duration of anticoagulation in unprovoked PE.

Duration of anticoagulation

A total of 41% of doctors said they would anticoagulate first-episode provoked PE for a 6- or 12-month period (Table 4). Most doctors (83%) would also recommend anticoagulation for fixed periods of 6 or 12 months for patients with unprovoked first-episode PE. For first-episode PE with active cancer, unprovoked second-episode PE and first-episode PE with significant irreversible risk factors other than cancer, the majority of doctors would recommend indefinite anticoagulation (81, 65 and 63% respectively).

Table 2

<table>
<thead>
<tr>
<th>Total (%)</th>
<th>Haematologists (%)</th>
<th>Respiratory physicians (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctors who are familiar with the ACCP’s 2012 guidelines (n = 164)</td>
<td>54.3</td>
<td>73.9</td>
<td>41.9</td>
</tr>
<tr>
<td>Doctors who agreed they base clinical decisions on a discussed guideline (n = 163)</td>
<td>76.7</td>
<td>85.9</td>
<td>70.7</td>
</tr>
<tr>
<td>Doctors who admitted familiarity with the PESI score (n = 146)</td>
<td>61.0</td>
<td>48.0</td>
<td>67.7</td>
</tr>
<tr>
<td>Doctors who frequently or always calculate and record the Wells score in patients suspected of having a PE (n = 162)</td>
<td>28.4</td>
<td>37.5</td>
<td>22.5</td>
</tr>
<tr>
<td>Doctors who frequently or always order cardiac biomarkers for patients with intermediate-risk PE (n = 141)</td>
<td>68.8</td>
<td>55.3</td>
<td>75.5</td>
</tr>
<tr>
<td>Doctors who frequently or always thrombolyse intermediate-risk PE with RVD on echocardiography and elevated troponin (n = 141)</td>
<td>16.3</td>
<td>27.7</td>
<td>10.6</td>
</tr>
<tr>
<td>Doctors who never or rarely thrombolyse high-risk PE in patients without contraindications (n = 142)</td>
<td>17.6</td>
<td>29.2</td>
<td>11.7</td>
</tr>
<tr>
<td>Doctors who generally discuss the risks and benefits of thrombolysis with their patients (n = 140)</td>
<td>90.0</td>
<td>82.6</td>
<td>93.6</td>
</tr>
<tr>
<td>Doctors who would recommend aspirin for patients with unprovoked PE who are ceasing anticoagulation (n = 137)</td>
<td>40.1</td>
<td>54.4</td>
<td>33.0</td>
</tr>
<tr>
<td>Doctors who frequently or always use D-dimer tests to guide the duration/continuation of anticoagulation in unprovoked PE (n = 143)</td>
<td>18.2</td>
<td>30.4</td>
<td>10.3</td>
</tr>
</tbody>
</table>

ACCP, American College of Chest Physicians; n, sample size; PE, pulmonary embolism; PESI, pulmonary embolism severity index; RVD, right ventricular dysfunction.

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Discussion

The survey revealed considerable variability in VTE management practices across multiple areas. Some of this variation may be because of discrepancies and gaps in recommendations from the ATG, NICE, ESC and ACCP as 77% of respondents said they base management decisions on one or more of these guidelines. Table 5 describes some of the areas where recommendations are absent or vary between these publications.⁴

Table 3 Multivariate logistic regression results showing variables associated with survey responses

<table>
<thead>
<tr>
<th>Doctors response</th>
<th>Variable</th>
<th>OR</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctors who are familiar with the ACCP’s 2012 guidelines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who are familiar with the ACCP’s 2016 guidelines</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Doctors who are familiar with the ESC guidelines</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who never or rarely thrombolys high-risk PE in patients without contraindications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who frequently or always thrombolys intermediate-risk PE with RVD on echocardiography and elevated troponin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who would anticoagulate first-episode provoked PE for 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who are familiar with the Wells score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who frequently or always calculate and record the Wells score in patients suspected of having a PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who admitted familiarity with the PESI score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who frequently or always use the PESI for initial assessment of PE severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who frequently or always use cardiac biomarkers for initial assessment of PE severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who frequently or always use imaging‡ for the initial assessment of PE severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who frequently or always order cardiac biomarkers for patients with intermediate-risk PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who generally discuss the risks and benefits of thrombolysis with their patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who recommend cardiac monitoring in patients with elevated troponin and RVD on CT or echocardiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who recommend cardiac monitoring for patients with RVD on CT or echocardiography but without elevated troponin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who frequently or always use D-dimer tests to guide the duration/continuation of anticoagulation in unprovoked PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctors who agreed they prefer NOAC over VKA for patients with PE without cancer or contraindications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

⁴Discussed guidelines were the American College of Chest Physicians: 9th edition, ACCP: 10th edition, The ESC, the National Institute for Health and Clinical Excellence or the Australian Therapeutic Guidelines. CT chest or echocardiography. ACCP, American College of Chest Physicians; CI, confidence interval; CT, computed tomography; ESC, European Society of Cardiology; NOAC, new oral anticoagulants; OR, odds ratio; PE, pulmonary embolism; PESI, pulmonary embolism severity index; RVD, right ventricular dysfunction; VKA, vitamin K antagonists.
For the purpose of this discussion, we have classified areas of variability in practice into three broad categories: areas of uncertainty, over-treatment and under-treatment. A practice was only considered over- or under-treatment if results deviated from a recommendation that is consistent across the three guidelines in Table 5. We acknowledge that more recent recommendations may be supported by better evidence.

**Areas of uncertainty**

**Weighing patients’ preferences**

Patients’ preferences for thrombolysis in intermediate-risk PE are important because of the nature of the risks, including debilitating stroke and intracranial haemorrhage, and benefits of treatment. Surprisingly, 10% of doctors reported that they do not discuss the risks and benefits of thrombolysis with their intermediate-risk patients, and 22% of those who do said patient preferences do not influence their decision to thrombolys “much or at all”.

**Thrombophilia and cancer screening in first-episode unprovoked PE**

The results indicate that thrombophilia screening for patients with first-episode unprovoked PE is ordered with varying frequency. This is consistent with findings from an American retrospective study which showed that thrombophilia testing is performed in an unstructured manner. Guidance in this area is limited (Table 5), and epidemiological data from the German MAISTHRO registry and multination REITE registry did not clearly identify patient groups who will benefit from testing. It is also unclear if test results are altering management decisions.

With regards to cancer screening, 12% of doctors do not regularly recommend being up-to-date with national screening programmes, while 17% regularly order a screening CT abdomen/pelvis in over 40-year olds. The NICE guidelines recommend the consideration of a screening CT abdomen/pelvis in patients over 40 years if initial investigations for cancer are negative; however, several more recent publications do not.
Table 5  Comparison of current guideline recommendations published by National Institute for Health and Care Excellence (NICE), the European Society of Cardiology (ESC) and the American College of Chest Physicians (ACCP)

<table>
<thead>
<tr>
<th>Duration of anticoagulation</th>
<th>NICE3</th>
<th>ESC4</th>
<th>ACCP 20165</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoked first-episode PE</td>
<td>3 months</td>
<td>3 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Unprovoked first-episode PE</td>
<td>Minimum 3 months with extended anticoagulation after assessment of recurrent VTE and bleeding risk</td>
<td>Minimum 3 months with extended anticoagulation to be considered if low bleeding risk</td>
<td>Minimum 3 months with indefinite anticoagulation† provided low/moderate bleeding risk</td>
</tr>
<tr>
<td>Provoked second-episode PE</td>
<td>No specific recommendation. See recommendation for first-episode unprovoked PE</td>
<td>Indefinite anticoagulation†</td>
<td>Indefinite† for low/moderate bleeding risk; 3 months for high bleeding risk</td>
</tr>
<tr>
<td>Unprovoked second-episode PE</td>
<td>No specific recommendation</td>
<td>No specific recommendation. However, the discussion says patients with thrombophilia† can be considered for indefinite anticoagulation† after a first-episode unprovoked PE</td>
<td>No specific recommendation. However, the discussion says no single risk factor increases the relative risk of recurrent VTE enough to alter management over those otherwise specified</td>
</tr>
<tr>
<td>First-episode PE with irreversible risk factors other than cancer</td>
<td>No specific recommendation</td>
<td>No specific recommendation. However, the discussion says patients with thrombophilia† can be considered for indefinite anticoagulation† after a first-episode unprovoked PE</td>
<td>Indefinite anticoagulation†</td>
</tr>
<tr>
<td>First episode in the presence of active cancer</td>
<td>Six months, then re-assess and consider extending</td>
<td>Three to 6 months, consider indefinite anticoagulation†</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Thrombophilia screen after unprovoked PE</td>
<td>Consider antiphospholipid antibodies if ceasing anticoagulation. Screen for hereditary thrombophilias† if family history of VTE§ and ceasing anticoagulation</td>
<td>Not discussed</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Cancer screen after unprovoked PE</td>
<td>Hx, Ex, CXR, FBE, Ca2+, LFT, Urinalysis. Consider CT abdomen/pelvis in patients &gt;40</td>
<td>Screening may be restricted to Hx, Ex, basic laboratory tests and CXR</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Follow-up scans</td>
<td>Not discussed</td>
<td>Routine VQ scan not recommended. If persistent dyspnoea, evaluation for CTEPH with VQ scan should be considered. No other recommendations</td>
<td>Not discussed</td>
</tr>
<tr>
<td>NOAC for management of VTE</td>
<td>VKA are recommended over NOAC. Rivaroxiban may be considered</td>
<td>NOAC should be considered as alternatives to VKA</td>
<td>NOAC recommended over VKA</td>
</tr>
<tr>
<td>Thrombosis for intermediate-risk PE</td>
<td>Do not offer thrombosis to patients with intermediate-risk PE</td>
<td>Thrombosis for intermediate-risk PE is not recommended unless there are signs of haemodynamic decompensation¶</td>
<td>Thrombosis for intermediate-risk PE is not recommended unless there are signs of deterioration††</td>
</tr>
<tr>
<td>Thrombosis for high-risk PE</td>
<td>Thrombosis should be considered</td>
<td>Thrombosis is recommended</td>
<td>Thrombosis is recommended in patients without high bleeding risk</td>
</tr>
<tr>
<td>Anticoagulation of asymptomatic SSPE</td>
<td>Not discussed</td>
<td>No specific recommendation</td>
<td>Not recommended unless there is concomitant DVT or a high-risk of VTE recurrence</td>
</tr>
<tr>
<td>Early discharge of low-risk PE</td>
<td>Not discussed</td>
<td>Consider early discharge and home treatment over inpatient stays of five days or more</td>
<td>Home treatment or an inpatient stay of fewer than five days is recommended over an inpatient stay of five days or more</td>
</tr>
<tr>
<td>Aspirin after cessation of anticoagulation for unprovoked PE</td>
<td>Not discussed</td>
<td>Aspirin should be considered</td>
<td>Aspirin is recommended</td>
</tr>
</tbody>
</table>
Australian guidelines could unify the approach and may reduce unnecessary screening.

**Aspirin use**

The ACCP’s 2016 guidelines recommend aspirin for patients ceasing anticoagulation for an unprovoked PE (Table 5). This recommendation is supported by two RCT published in 2012. Despite this, only 40% of respondents recommend aspirin in this instance.

**Management of low-risk PE**

The survey showed that 66% of doctors would anticoagulate patients with asymptomatic SSPE without concomitant DVT. These findings are consistent with those of a 2013 European survey. The ACCP’s 2016 guideline recommends that these patients should not receive anticoagulation (Table 5). There are no published RCT on the subject, and the other guidelines do not make a recommendation.

**Follow-up scans**

A total of 16% of doctors routinely request echocardiograms during the follow up of individuals with unprovoked PE. Routine use is unlikely to be beneficial for identifying chronic thromboembolic pulmonary hypertension (CTEPH), although two moderate-sized cohort studies indicate that follow-up echocardiography may be useful to diagnose CTEPH in a subset of patients. The ESC’s guideline has recommendations for follow-up screening of patients at risk of CTEPH, although none of the guidelines consider follow-up imaging for other indications (Table 5). A total of 35% of respondents order a VQ scan for routine follow up on cessation of anticoagulation after unprovoked PE. Evidence regarding the usefulness of follow-up imaging to tailor anticoagulation duration is limited. A small study from 2015 found that the risk of recurrent VTE was not associated with residual thromboembolic obstruction on CT. However, VQ single photon emission CT may be useful for tailoring the duration of anticoagulation based on the resolution of perfusion defects.

Further research is required to establish the utility of ordering tests in this situation.

**Areas of uncertainty in duration of anticoagulation**

Anticoagulation practices were variable for unprovoked second-episode PE and first-episode PE with significant irreversible risk factors other than cancer. Discrepancies in guideline recommendations broadly reflect this (Table 5). These results are consistent with findings from the European REITI registry, which found heterogeneous anticoagulation practices.

**Areas of under-treatment**

The major guidelines recommend using thrombolysis for high-risk PE unless the patient has a clear contraindication (Table 5). However, the results of this survey suggest that there is a level of under-treatment of high-risk PE by some physicians, which is consistent with results from overseas studies. Analysis of the American EMPEROR registry showed that in the period 2006–2008, only 7 of 58 patients admitted with high-risk PE received thrombolysis. This study also found a trend of reduced mortality in the thrombolysis group compared with those who did not receive thrombolysis, although the study was underpowered to detect a true difference. A European study found similar results.
There was also a tendency to under-treat first-episode unprovoked PE. The majority of physicians surveyed (73%) said they would recommend anticoagulation for periods of 6 or 12 months (Table 4) despite guidelines recommending indefinite anticoagulation\(^a\) (Table 5).\(^{5,5}\)

**Areas of over-treatment**

A significant proportion of doctors surveyed (41%) indicated that they would anticoagulate first-episode provoked PE for a period of 6 or 12 months despite consistent guideline recommendations for 3 months of anticoagulation (Table 5). Results from the REITE registry study suggest that such variable anticoagulation practices may increase the risk for fatal bleeding.\(^6\)

Our survey also suggested over-treatment in the management of intermediate-risk PE, although to a lesser degree. In particular, 16% of doctors surveyed indicated that they would frequently or always recommend thrombolysis for normotensive patients with elevated cardiac biomarkers and evidence of RVD on echocardiogram (Fig. 1), with haematologists four times more likely than respiratory physicians to make this recommendation (Table 2). However, guidelines recommend that thrombolysis be considered for this group of patients only if there is haemodynamic or clinical deterioration (Table 5).

**The Australian context**

Our findings are consistent with the Care Track Australia study, which showed that the level of compliance with guidelines for VTE prevention and management requires improvement.\(^11\) Efforts have been undertaken by the National Health and Medical Research Council to implement VTE prophylaxis strategies across Australia\(^29\); however, these strategies have not included the management of acute VTE. A 2014 study of post-surgical VTE in New South Wales suggested that urgent policy action on all VTE management is required as the mortality rate of VTE had not changed over the period of 2002–2009.\(^30\)

**Limitations**

The major limitation of this study was the low response rate. However, the survey respondents’ demographic distribution is consistent with national data,\(^31,32\) and we believe the sample represents an adequate cross-section of haematologists and respiratory physicians.

Considerable effort was made to increase the response rate, including multiple reminders and attendance at scientific meetings. Although a high response rate is preferable, non-response rate is not a good indicator of the size of non-response bias alone,\(^13,14\) and our rate is similar to other surveys of Australian doctors.\(^15–17\)

**Implications for practice and future research**

This survey highlighted key areas of over-treatment, under-treatment and uncertainty in VTE management. The development and implementation of a national evidence-based clinical practice guideline may reduce this variability and improve VTE management in Australia. There are many areas where clinical uncertainty exists because of gaps in the evidence base, which may be addressed by future research; however, in the interim, consensus statements may discourage an excessive reliance on tests of unclear utility and may help to facilitate the development of unified treatment pathways. This study provides data on which areas guidelines need to focus. In addition, it is likely that specific interventions will be needed to promote the uptake of guidelines and encourage behavioural change.

VTE is a common condition managed by general practitioners, emergency physicians, general physicians, specialist physicians and surgeons. It is important to engage all relevant clinicians and stakeholders for guideline development, and future surveys of VTE management should include practitioners not covered by this survey.

Future prospective cohort studies that link management practices to patient outcomes will provide data about variations in practice and outcomes. One study has been established, but larger studies, including multiple centres are needed.\(^38,39\) Guideline development could also facilitate the development of nationally standardised audit tools to evaluate VTE management.

**Conclusion**

This survey of respiratory physicians and haematologists has demonstrated significant variability in VTE management, some of which relates to areas of clinical uncertainty that are either not covered by current guidelines or for which guideline recommendations are inconsistent. There were also deviations from consistent guideline recommendations; in particular, there is evidence of over-treatment of patients with provoked PE and patients with intermediate-risk PE and under-treatment of patients with high-risk PE. The findings highlight the urgent need for the development and implementation of national guidelines for the management of VTE in Australia.

*Minimum 3 months anticoagulation followed extended anticoagulation until the clinical risk of recurrent VTE no longer outweighed the risk of bleeding.*
Acknowledgements

We acknowledge those physicians who provided feedback during the drafting of the survey. We are also grateful to the TSANZ, the Australasian Society of Thrombosis and Haemostasis and the HSANZ for their assistance with the distribution of the survey.

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Supporting Information

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

Appendix S1. Questionnaire.
Using iron studies to predict HFE mutations in New Zealand: implications for laboratory testing

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Key words
hereditary haemochromatosis, HFE gene, iron, transferrin, hyperferritinaemia.

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Abstract
Background: The diagnosis of hereditary haemochromatosis (HH) is not straightforward because symptoms are often absent or non-specific. Biochemical markers of iron-overloading may be affected by other conditions.
Aim: To measure the correlation between iron studies and HFE genotype to inform evidence-based recommendations for laboratory testing in New Zealand.
Methods: Results from 2388 patients genotyped for C282Y, H63D and S65C in Wellington, New Zealand from 2007 to 2013 were compared with their biochemical phenotype as quantified by serum ferritin (SF), transferrin saturation (TS), serum iron (SI) and serum transferrin (ST). The predictive power of these markers was evaluated by receiver operator characteristic (ROC) curve analysis, and if a statistically significant association for a variable was seen, sensitivity, specificity and predictive values were calculated.
Results: Test ordering patterns showed that 62% of HFE genotyping tests were ordered because of an elevated SF alone and only 11% of these had a C-reactive protein test to rule out an acute phase reaction. The association between SF and significant HFE genotypes SF was low. However, TS values ≥45% predicted HH mutations with the highest sensitivity and specificity. A SF of >1000 μg/L was found in one at-risk patient (C282Y homozygote) who had a TS <45%.
Conclusion: Our analysis highlights the need for clear guidelines for investigation of hyperferritinaemia and HH in New Zealand. Using our findings, we developed an evidence-based laboratory testing algorithm based on a TS ≥45%, a SF ≥1000 μg/L and/or a family history of HH which identified all C282Y homozygotes in this study.

Introduction
Hereditary haemochromatosis (HH) is a common autosomal recessive disorder associated with pathogenic HFE gene variants that may cause a disorder of iron metabolism characterised by an increased, inappropriate absorption of intestinal iron.1,2 Over time, iron accumulation in tissues can cause irreversible organ damage leading to cirrhosis, diabetes, arthritis, cardiac dysfunction and impotence. However, it is rare, nowadays, to encounter advanced clinical disease and is usually seen in individuals with a serum ferritin (SF) concentration exceeding 1000 μg/L.1 Chronic fatigue is the most common finding and may be an early indicator of the disease.1 Therapeutic phlebotomy is a simple and effective way of normalising the iron concentrations and if implemented at an early stage, can result in a normal life expectancy for the affected individual.3,4

HH is the most common identified genetic disease in Caucasians and arises mostly in males between 40 and 60 years of age.5,6 It is common in individuals of northern European origin with an approximate carrier frequency of 1 in 10 people affected.7 Its incidence is distributed worldwide, and it is estimated that 1 in 200 individuals in Australia and New Zealand are homozygous for C282Y, the most common single nucleotide polymorphism (SNP) found on the HFE gene.8 However, the HFE genotypes show variable phenotypic expression suggesting that other genetic and environmental factors may contribute to iron loading.3 A proportion of C282Y homozygotes may not develop significant clinical sequelae (approximately 30%)5 and conversely, several C282Y carriers (approximately 1–6%) may develop overt disease.4 Therefore, management does not rely solely on genetic diagnosis; it also
relies on evidence of biochemical and clinical phenotypic expression.3,5

Although there is strong evidence to justify the need for pre-symptomatic detection of this condition, one of the problems faced by primary care physicians in identifying HH is that symptoms are often absent or mimic those found in other common conditions. The international consensus is that population screening for HH is not recommended for reasons, including cost effectiveness, insurance discrimination5 and the low penetrance of the C282Y mutation.9,10

Abnormalities in iron biochemical assays are often the first indicator of HH, and it is widely accepted that transferrin saturation (TS) and SF are the best initial tests for HH.5,6,8,11,12 However, the iron studies results for serum iron (SI), serum transferrin (ST), TS and particularly SF may be affected by other conditions, such as the acute phase response, obesity or fatty liver disease. As a result, the predictive power of SF for HH is diminished in Caucasians and indeed non-alcoholic fatty liver disease and alcohol ingestion are the most common causes of elevated SF levels rather than C282Y-linked HH.13,14 Prevalently undiagnosed C282Y homozygotes with SF values that remain <1000 μg/L are at low risk for developing HH signs and symptoms.14 While treatment is usually not advocated in these patients, a recent French study showed that venesection may reduce mortality in individuals, such as those with moderately elevated ferritin.15 Therefore, the interpretation of iron studies results in both predicting and treating HH can be difficult and is often controversial and/or misunderstood.

In the Wellington region of New Zealand, from 2007 to 2015, genotyping of HFE SNP that cause the amino acid substitutions commonly associated with HH (C282Y, H63D and S65C) was performed on request without the requirement for iron studies or other risk factors. A retrospective audit of HFE genotyping and available iron studies results was performed to identify any correlations that could be used to improve the proportion of requested tests with C282Y homozygosity. Incorporation of these data into a New Zealand-specific testing algorithm for HH diagnosis would provide valuable guidance for local primary care physicians in selecting and interpreting laboratory tests.

Methods

Patients

The data used in this study were derived from the test results of 2388 patients who had HFE genotyping performed in Wellington, New Zealand, from 22 May 2007 to 31 July 2013. All patients were referred for testing from the community by their general practitioner or specialist and were not acutely ill. For statistical analysis, subjects were included if they were at least 18 years of age and had either a SF test only or a full iron studies profile (TS, SF, SI and ST) performed within the 3 months preceding HFE genotyping. Patients with evidence of inflammation (elevated C-reactive protein (CRP)) were identified. Antenatal patients were excluded from the analysis.

Biochemical and haematological measurements

SI, ST and CRP tests were performed on fresh serum samples by immunoturbidimetric methods on the Roche Modular P800 (Sydney, NSW, Australia). TS was calculated using the algorithm based on SI and ST and SF was performed on fresh serum samples by a sandwich electrochemiluminescence (ECL) immunoassay on the Roche Modular E170.

HFE genotyping

Human genomic DNA was extracted from whole blood ethylenediaminetetraacetic acid using the MagNAPure LC instrument (Roche) with the DNA I extraction protocol. Multiplex real-time polymerase chain reaction amplification was performed on the LightCycler 480 v1.0 (Roche) using primers (Integrated DNA Technologies, Coralville, IA, USA) and hybridisation probes (TIB MolBiol, Berlin, Germany) specific for C282Y and H63D. The same primers and probes designed for H63D were used to detect the S65C mutation since these SNP are localised within nine base pairs of each other and thus the detector probe overlaps codon 63 and codon 65. The SNP were identified using melting curve analysis on the LightCycler 480 software V1.5 (Roche).

Statistical analysis

The subjects’ iron studies profile results were stratified, and analyses were performed based on gender and in females, age less than or greater than 56 years to distinguish between pre- and post-menopausal women. To evaluate the performance of TS, SF, SI and ST in correlating with HFE genotype, receiver operator characteristic (ROC) curves were calculated in SPSS statistical software (Chicago, IL, USA). The predictive power of each independent variable to identify specific HFE genotypes was compared with patients with wild-type genotypes for C282Y, H63D and S65C (disease negative). ROC curves were not performed on any genotype groups with
less than five subjects. If a statistically significant association for a variable was seen in ROC curve analysis (area under the curve (AUC) >0.5; $P < 0.05$), the sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated at varying intervals, chosen relative to the reference range established for our laboratory (shown in Table 3).

**Results**

**Genotype frequencies**

$HFE$ genotyping was performed on a total number of 2874 subjects from 22 May 2007 to 31 July 2013. Of these, 489 (17%) had clinically significant $HFE$ genotypes, including C282Y homozygosity (C282Y/C282Y), C282Y compound heterozygosity (C282Y/H63D or C282Y/S65C) and H63D homozygotes (H63D/H63D); while 2385 (83%) had other $HFE$ genotypes or were unaffected.

Of the original 2874 patient results audited, a total of 2388 patients had a SF test performed in the 3 months prior to $HFE$ genotyping and thus were included in this study. Of these, 912 patients (38%) had a full iron studies profile performed. Genotype frequencies and patient demographics are shown in Table 1.

**Test ordering patterns**

For data analysis, the iron studies results performed in the 3 months prior to genotyping were divided into two sets: patients who had a SF test ($n = 2388$) and patients who had a full iron studies profile (TS, SF, SI and ST) performed ($n = 912$). The difference between the two data sets indicates that a total number of 1476 subjects (62%) had $HFE$ genotyping performed driven by an abnormal SF result, without a full iron studies profile. Furthermore, it was found that only 11% (263 subjects) had a CRP test performed, which suggests other causes of elevated SF are not being investigated. Excluding patients who had laboratory evidence of infection or inflammation (CRP $>7$ mg/L) was therefore not possible.

**ROC curve analysis**

ROC curves were generated for each of the iron studies parameters in the diagnosis of specific combinations of $HFE$ genotypes. In ROC curve analysis, TS showed the strongest association overall in each of the $HFE$ genotype cohorts, with the AUC reaching 0.957 in the male C282Y homozygous group (Table 2). The performance of SI correlates closely with that of TS. SF, as a predictor of...
The best sensitivity achieved by SF was at the upper limit of normal for each gender (150 μg/L females <50 years, 400 μg/L males and females >50 years), although with a very low specificity being produced. Similarly, when high specificity was achieved, this was paralleled by a compromised sensitivity. Although the NPV for SF reached 80% in some cohorts, the associated PPV for SF was extremely low, underlining the inefficiency of SF values up to 1000 μg/L as a single predictor of HFE genotype. For TS, there was a marked improvement in sensitivity, specificity and NPV, with a cut-off of 45% producing the most favourable outcome. SI was relatively insensitive to genotype in the female groups and although this improved in the male group, this parameter on its own appears to lack the power achieved using the TS calculation. Using a TS threshold of 45%, there were eight misidentified C282Y homozygous patients (false negatives). Seven of these patients were tested on the basis of family history and clinical details did not indicate any manifestations of the disease, thus were considered phenotypically normal. However, the one misidentified female aged 56–92, had clinical details of ‘Very high SF (1887 μg/L) and weight loss’. Excluding this patient from testing may have clinical implications because this patient is post-menopausal, increasing the risk of iron overload.

Laboratory testing recommendation

Using the findings of statistical analysis in this study, the following testing recommendation for New Zealand pathology laboratories is suggested:

Perform HFE genotyping when:
- TS ≥ 45% or ferritin ≥1000 μg/L in either males or females.
- SF is elevated AND TS ≥ 45% AND further testing, including evaluation of environmental factors (such as alcohol intake, infection/inflammation presence of metabolic syndrome) has ruled out other causes of elevated SF.
- In patients who have a first-degree relative who is a C282Y homozygote or who have had testing overseas, for example, 23andMe.

Discussion

Homozygosity for the C282Y SNP of the HFE gene is diagnostic of HH; however, it is not considered cost-effective to screen patients with molecular testing unless there is sound clinical, familial or biochemical evidence to indicate testing. There is currently no New Zealand
Table 3
Decision points and predictive value of iron studies parameters compared to HFE genotype

<table>
<thead>
<tr>
<th>Iron studies parameter</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Decision point</th>
<th>Sensitivity % (SP/TP)</th>
<th>Specificity % (SN/TN)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gp. 1</td>
<td>Gp. 2</td>
<td>Gp. 1</td>
<td>Gp. 2</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>Female</td>
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<td>45</td>
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<td>55.56 (10/18)</td>
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<td>45</td>
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<td>59.09 (13/22)</td>
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<td>40.91 (9/22)</td>
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<td>45</td>
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<td>18–55</td>
<td>30†</td>
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<td>30†</td>
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<td>40</td>
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<td>17.14 (18/105)</td>
<td>98.16</td>
<td>98.16</td>
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<tr>
<td>Serum ferritin (μg/L)</td>
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<td>150†</td>
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<td>57.58 (78/135)</td>
<td>26.97</td>
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</table>

†Upper limit of normal reference range. SP/TP, screen positive out of total positive as identified by HFE genotyping; SN/TN, screen negative out of total negative as identified by HFE genotyping; PPV, positive predictive value; NPV, negative predictive value; Gp. 1, C282Y homozygous (C282Y/C282Y); Gp. 2, C282Y homozygous (C282Y/C282Y), C282Y compound heterozygous (C282Y/H63D) or C282Y/H63D and H63D homozygous (H63D/H63D).
national guideline for requesting HH testing, although non-binding recommendations based on international data have been published. In this study, we measured the correlation between biochemical penetrance and HFE genotype in order to develop laboratory testing recommendations for HH for New Zealand.

The patients included in our study were enriched for C282Y homozygotes (6.2 cf 0.5%) and compound heterozygotes (8 cf 1.8%) compared with a previous study from Christchurch, New Zealand. However, our sample size of 2388 is the largest retrospective study linking genotype with SF, TS and SI in HH affected and unaffected New Zealanders to date.

The main weakness of this study is that it is retrospective data, and lacks significant clinical information on our patient cohort and as a result, only the biochemical phenotypic characteristics of the disease could be included in the laboratory testing algorithm. In addition, ethnicity could not be controlled for. In the extensive HEIR study, a large number of Asian and Pacific islanders showed increased SF and TS in the absence of iron overload, suggesting that the results for these populations may need to be interpreted differently than for Caucasians. Further studies are needed given the multietnic population in New Zealand, which includes Māori, Pacific Island and Asian populations.

By linking genotype data to SF, TS and SI in 2388 patients, we calculated the performance of these measures for predicting the presence of this inherited disorder in our local population. We found that the Best Practice Advocacy Centre New Zealand (BPACNZ) advice that SF >700 μg/L is an indicator of HH was inaccurate. Using ROC curve analysis we showed that sensitivity, specificity and predictive values for SF values up to 1000 μg/L were poor predictors for all clinically significant HFE genotypes, and this is supported by other international studies. The NPV of SF was high overall and thus this marker was effective at ruling out subjects with an unaffected genotype. However, in the absence of controlled trials it is not known whether subjects with SF <1000 μg/L are or can be symptomatic. The SI and TS are usually normal suggesting that the raised ferritin is part of a reactive acute phase response.

Our study showed that TS is the best predictor of clinically significant HFE genotypes in our testing population, in line with published data. A marked improvement in PPV and NPV was observed compared to that of SF analysis, with a higher proportion of subjects with clinically significant genotypes being correctly identified by their TS. Since SI is used in the testing algorithm to calculate TS, it was not surprising that the two markers had a similar performance in ROC curve analysis. However, SI is known to have a high diurnal variability, which may help to explain why its sensitivity was poor in all cohorts at cut-offs above the normal range (>30 μmol/L). For this reason, SI alone proved to be an ineffective screening test for HH.

Our analysis showed that a TS decision threshold of 45% was the most reliable indicator of HH, in agreement with that recommended by many for consideration of HFE genotyping. However, Oglivie et al. recommended a TS threshold of 50%, which if applied to our data would have incorrectly classed a further two C282Y male homozygotes as negative. A high threshold may compromise patient safety, underscoring the need for local analysis of biochemical penetrance before suggesting testing guidance.

However, had we solely used a TS threshold of 45% for performing HFE genotyping, eight C282Y homozygous patients would have been missed. Seven of these had a family history of HH, which corroborates current best practice guidelines from the European Molecular Quality Network and BPACNZ with regard to the importance of HFE testing on this basis. The one remaining misidentified C282Y homozygote (female) had a SF of 1887 μg/L and would have been missed if genotyping recommendations did not include an SF of >1000 μg/L as a criterion, as she had no other markers of iron overload.

Despite various international guidelines that recommend TS testing ahead of HFE genotyping for diagnosing disease, the majority of subjects (62%) in this study appear to have had HFE genotyping performed on the basis of a SF result alone, without TS. This is consistent with two recent UK-based studies and demonstrates a wide lack of adherence to best practice guidelines. Establishing the cause of hyperferritinaemia in some patients remains a dilemma for many physicians, however relatively expensive HFE genotyping should not be considered without prior consideration of other more common causes of elevated SF. Indeed, Francis and Thachill showed in a small study (n = 231) that using TS threshold of >50% to triage HFE testing would have saved the laboratory >30 000 in unnecessary testing over 2 years based on costings of £181 per HFE test.

Although a HFE test in New Zealand is significantly cheaper (NZ$87 or £41 approximately), our screening strategy produces a similar outcome, with a cost saving of $34 626 (£16 314 approximately) over the duration of this study. An important difference between the two triaging strategies is that ours included SF >1000 μg/L and family history as predictors, as well as a lower TS threshold of 45%. This may reduce the potential savings, however represents a more clinically appropriate strategy since it correctly identified all C282Y homozygotes.

Diurnal fluctuations have been described primarily for SI, from which TS is calculated. In the HEIR study, it
was shown that initial phenotyping with TS could miss approximately 30% of cases. While that was not the case for the current study, the HEIR data underline the importance of including elevated SF and symptoms in the algorithm for HFE genotyping. We too, would have misidentified one at-risk patient had we relied solely on TS as a predictor. In addition, local clinicians clearly hold SF as being significant. So, although incorporating SF into our testing algorithm is costly in terms of the high false positive rate as indicated by the low specificity values, there is still be a place for this parameter in a local diagnostic screening strategy for HH.

Using our findings, we have developed an evidence-based laboratory testing algorithm for HH in New Zealand that is based on SF, TS and family history. The implication of this testing algorithm is that some patients with subclinical HH may be missed as these genotypes show variable phenotypic expression. It is important therefore that patients with significant unexplained symptoms are not precluded from testing based on this testing algorithm; however, the decision should be determined at a higher level than general practice. Such a clinical pathway could be used by primary care physicians and laboratory staff to provide a targeted and cost-effective strategy for HH screening in New Zealand.

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Prescribing and medication communication on the post-take ward round

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BRIEF COMMUNICATIONS

Prescribing and medication communication on the post-take ward round

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Key words
prescribing, handover, communication, hospital, ward round, patient safety.

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Prescribing, a complex and challenging task, is often suboptimal in hospitals where over-, under- and inappropriate prescribing is well recognised.1 This can result in errors and unacceptable patient outcomes, including adverse drug events (ADE).2

On post-take ward rounds (PTWR), junior medical officers (JMO) present each newly admitted patient to the consultant. During this PTWR, diagnosis is often established, and the treating team make decisions about investigations and treatment, including the need for medication changes.3,4 The consultant is responsible for final management decisions, whilst the JMO often implements these decisions.3 This separation of tasks increases the risk of prescribing errors as JMO often lack the competence and confidence to prescribe appropriately.6–8

Factors contributing to JMO prescribing errors are complex and include a lack of drug knowledge, inadequate supervision and communication.7 One study identified significant gaps in the detail of conversations and inappropriate assumptions made by JMO regarding prescribing.3

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Conflict of interest: None.

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The details of medical officers (MO) communication, decisions and their actions on the PTWR are poorly understood.

This study aims to describe medication-related communication between MO on internal medicine PTWR, medication decisions made and the extent to which they are implemented.

The study also investigated whether discussions focused on medications with a higher risk of harm.

An observational, prospective, cohort study was conducted where medication-related communication was observed during daily internal medical PTWR over a 6-week period in 2014 at a quaternary teaching hospital in Brisbane, Australia. During the study, a standard clinical pharmacy service was available on weekdays.

Each ward round had a single data collector (trained clinical pharmacist with 9 years of hospital experience and postgraduate training) whose role was purely observational unless an intervention was required to prevent or highlight a potential severe error. A data collection tool was developed, which underwent structured review and user trials to ensure the reliability and accuracy of documentation regarding prescribing and communication. The data collected were subsequently reviewed by a senior pharmacist and senior MO to ensure clarity around each data point collected.

All members of the eight medical teams provided informed consent to be observed.

Patients eligible for recruitment were those who were 16 years or older. For pragmatic reasons, observations occurred on a convenience sample of patients seen 4 days a week from 8 am to 11 am.

Data collected included patient demographics, comorbidities, number of medications prescribed and time spent with each patient. All medication-related discussions were recorded and classified as either a ‘minimal medication discussion’, defined as only a mention of the medication and/or some detail (such as the dose or route), or an ‘in-depth medication discussion’ where modification was considered. For each discussion, the level of MO (consultant, registrar, JMO) initiating discussion and proposing, confirming and implementing the plan was recorded. Any non-medical officers who entered PTWR discussions were classified as ‘other’.

Subsequent to PTWR, prescriptions and discharge medication records (DMR) were reviewed for evidence of medication changes proposed on the PTWR.

All medications were categorised as high or low risk of medication-related harm according to the Australian Safety and Quality Council’s A-PINCH classification system. Analysis was undertaken using Microsoft Excel and R3.3.1. Patient demographics and other continuous data are presented as mean ± standard deviation (normal) or as a median (range) for non-normal data. Categorical and binary data have been expressed as counts and percentages of the total number of possible outcomes. Chi-squared tests were used to compare proportions between groups.

During the 6-week period, 24 PTWR and 130 patient consultations were observed. A total of 41 MO was observed: 11 consultants, 11 registrars and 19 JMO. There was an average of four MO per PTWR (range 4–6), with a median of three observations per team and between four and six JMO present on each PTWR. The mean duration of a patient review was 23 ± 8 minutes (range 7–53 minutes).

Of the 130 patients observed, 53% were male, and 58% were ≥65 years old; their mean age was 66 years (SD 19). The mean number of comorbidities per patient was 6.1 (SD 3.3). The most frequent classifications of patients using the Australian Refined Diagnosis Related Group were ‘syncope and collapse’, chest pain” and ‘kidney and urinary tract infection’.

For the 130 patient consultations, 1244 medications were charted prior to or following the PTWR, a median of nine medications/patient (range 0-31). Of these, 811 (65.2%) were mentioned on the PTWR (Fig. 1). A DMR was available for 80 (62%) patients and provided the final list of discharge medications. For those patients with a DMR, the median number of medications on discharge was nine per patient (range 1–28).

Medication-related allergies and ADR were discussed in 48 (37%) patients and adhered to in 19 (14.6%).

Table 1 shows details of the medications discussed for those with ‘minimal medication discussion’ and the role of each MO.

Of the 1244 medications charted prior to or following the PTWR, 30% (n = 374) of those mentioned were classified as ‘high risk’, a similar proportion to those that were not high risk (30%, n = 245).

There were 249 in-depth discussions relating to 126 medications, an average of 1.9 per patient. Of these discussions, 152 (61%) were initiated by the consultant and 78 (31.7%) by the registrar. The consultant suggested resolution for 158 (63.4%) of these.

Of the 249 in-depth discussions, 58 agreed changes were unable to be incorporated on the PTWR. Of the remaining 191 agreed actions, 153 (80%) were implemented on the PTWR; 21 (11%) were implemented later; and 17 (9%) were never implemented. Of those implemented, 93 (60.8%) of the recommendations were carried out by registrars and 51 (33.3%) by JMO.
Discussion

This study has identified a number of clinical gaps in medication communication and the implementation of agreed medication-related management decisions.

Importantly, less than two-thirds of all prescribed medications were mentioned on the PTWR, with only 10% being discussed in detail. Given that there was no difference in the degree of communication dependent on the A-PINCH criteria, it is unlikely that it was merely the less important medications that were not discussed. This lack of in-depth discussion suggests a missed opportunity to review whether patients’ medications taken prior to admission may have been associated with an ADE or may have contributed to that admission.

Of concern, one in 10 clinical decisions made on the PTWR was not implemented, with potential adverse patient outcomes. For example, a decision was made to start oral anticoagulants in one patient with atrial fibrillation who was clinically indicated for this treatment; however, this did not occur during the admission and/or was recommended on discharge. Registrars were the most common participant to mention or hand over medications on the PTWR; however, consultants were most likely to make treatment decisions. JMO are often responsible for implementing decisions but rarely discussed medications on the PTWR. It is possible that JMO disengagement from these conversations has contributed to decisions not being appropriately implemented.
Of the medications discussed, indication and dose were rarely mentioned. These are important components of the medication review and reconciliation processes, which, if not undertaken effectively, may result in adverse outcomes.\textsuperscript{10} Patient adherence was infrequently discussed in spite of increasing evidence that adherence is positively linked to overall health costs,\textsuperscript{11} rate of hospitalisations\textsuperscript{12} and health outcomes.\textsuperscript{13} Overall, our findings suggest that limited consideration was given to when medications should be monitored, reviewed and/or stopped in the PTWR setting. This study highlights the opportunity for a system change to improve communication, prioritisation and implementation of medication-related decisions in order to optimise care, for example, participation of a medication-focused clinician using a structured medication review tool, such as the ‘Considerate Checklist’\textsuperscript{4} or the ‘Medication Management Plan’.\textsuperscript{14}

This study extends existing knowledge on medication discussions and prescribing on PTWR. Several areas where patient outcomes may be improved are worthy of exploration.

Ethics approval was obtained from the Hospital and University Human Research Ethics Committees (HREC/13/QRBW/443; 2014000705). Verbal consent was obtained and recorded for all patients whose PTWR consultation was observed in this study. Written informed consent was obtained from all MO prior to the period of observation. MO and patient consent could be withdrawn at any time.

Acknowledgements

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References

Compliance to clinical pathways in the management of suspected pulmonary embolus: are there cost implications?

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Key words
pulmonary embolism, cost implication, pretest probability, hospital/standard, clinical audit.

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Abstract
This study investigated the cost implications of poor compliance to established guidelines for management of suspected pulmonary embolism (PE) in two NSW public hospitals. A retrospective audit showed that the prevalence of PE overall was 9.9% (4.3% in the low-risk groups) in 436 patients. An estimated total of $32 454 (14%) was spent on unnecessary tests.

Pulmonary embolism (PE) remains a common and potentially preventable cause of death.1 Clinical guidelines have been established and consist of a clinical probability assessment calculated using the Wells score and D-dimer testing, then multi-detector computed tomography pulmonary angiogram (CTPA).2–9 The simplified Wells score is the most widely used clinical tool for pretest probability (PTP) for PE.6

The aims of this audit were to: (i) compare the diagnostic approach to PE observed to that of well-established clinical guidelines; (ii) conduct a cost analysis of D-dimers and CTPA used according to observed PE prevalence rates.

This was a retrospective audit of 436 consecutive CTPA requested in the emergency department medical wards in two NSW teaching hospitals: Wyong, a small rural hospital, and Wollongong, a larger NSW teaching hospital. From electronic clinical records we determined: (i) patient demographics; (ii) clinician-documented PTP using a validated prediction method – the simplified Wells score for PE; (iii) the quantitative D-dimer and result; and (iv) CTPA findings. We used a modified Wells score >4.0 as high risk and ≤4 as low risk. We adopted a similar methodology to Sud et al.10 This audit simply recorded the tests as used by the treating physicians. The study was subject to an institutional review and approval.

There were no significant differences in the demographics of patients presenting to each hospital. Student’s t-test and Chi-squared test for comparisons of continuous variables and proportions were used when looking for significant differences between the two hospital cohorts. We estimated the potential cost saving of adhering to a protocol using Wells score and D-dimer. Australian Medicare bulkbilling costs of CTPA (AU$510) and D-dimer (AU$77.56) were used in cost estimates and the differences in cost between observed investigation strategies and the standard protocol recommended in guidelines (Table 1). We estimated the overall cost per PE diagnosed at each hospital and performed a sensitivity analysis on costs11 by estimating 95% confidence intervals (CI) for observed D-dimer use in high risk groups (both sites 95% CI 13–31), and the per-protocol CTPA use in low risk group (Wyong 76, 95% CI 62–90; Wollongong 61, 95% CI 49–73) (Table 1).

Wyong hospital audit included 259 patients, of which 140 (55%) were female, and 149 (57%) were under 70 years of age. For the 177 patients in Wollongong hospital, 92 (52%) were female, 108 (61%) patients were under 70 years. As shown in Figure 1, in the low risk category D-dimer was performed in 110 patients. The prevalence of PE was 3.3% in the low-risk
group. The overall prevalence, in all patients investigated for PE, was 9.9%, (43/436).

In the high-risk group, all patients should have had CTPA without the need for D-dimer. We regarded any D-dimer performed in this group as unnecessary. In both Wyong and Wollongong hospitals combined, 44 patients had unnecessary D-dimers performed (Fig. 1). Table 1 shows the cost of not adhering to a given validated protocol at AU$32 453 combining the two study sites.

This was a retrospective audit conducted in two teaching hospitals in NSW, Australia. The overall prevalence of CTPA confirmed PE was 9.9%. There were 44 unnecessary D-dimers performed in the high risk groups, when the Wells score was clearly suggestive of high risk indicating the need to proceed to CTPA.

The Wells score and D-dimer are proven to reduce the number of CTPA performed on low-risk PE patients and has a very good negative predictive value. Overall in both hospitals the standard protocol was not followed for 40% of patients. There was confusion over the need to perform D-dimers in high risk patients, failure to perform D-dimers in low-risk patients, and undertaking CTPA when the patient was at low risk and D-dimer was low. This resulted in unnecessary testing of D-dimer and CTPA, inflating costs for the overall investigation strategy in both hospitals by 14% where a standard protocol was not followed.

Documentation of precise Wells score PTP was poor in both hospitals. Where the Wells score was mentioned in the clinical records, it was usually recorded as high or low with no numerical value. The introduction of a strict policy for documentation of Wells PTP and D-dimer resulting in appropriate PTP grouping has been shown to reduce significantly the number of CTPA performed in a Melbourne tertiary hospital. Such algorithms have been shown to be safe and cost-effective in clinical trial settings. This audit demonstrated gross underutilisation of the D-dimer assay as an exclusionary test for PE in low Wells PTP subjects undergoing CTPA. As a result, 32 CTPA in the low Wells PTP subgroup were unnecessary. A further 99 low Wells PTP subjects underwent CTPA without D-dimer testing; only two CTPA confirmed pulmonary emboli. This underutilisation of the D-dimer in those with a low PTP disregards the findings and conclusions from previous studies.

The overall prevalence of PE in our audit was significantly lower (9.9 vs 16.9% (480 of 2840 patients from four studies); P < 0.005) than in studies evaluating the usefulness of D-dimer test in combination with a clinical PTP score. However, it was similar to the PE prevalence in those with a low PTP, when compared with pooled data of patients undergoing CTPA across four other studies. This suggests Wyong and Wollongong hospitals have relatively easy access to CTPA and a lower threshold for suspecting PE. A very low Wells score should alert the clinician that their suspicion of PE may be unwarranted.

Our data and that of Yin et al. justify the need for cost analyses of D-dimers and lung scans in hospitals that have a high index of clinical suspicion for PE with correspondingly low PE prevalence. In the Yin et al. study, none of the 114 low PTP subjects who underwent CTPA had PE (upper 95% CI 9%). Our audit showed one positive PE each among the 72 (1.4%, 95% CI 0–4%) and 60 subjects (1.6%, 95% CI 0–5%) with low PTP where the D-dimer was low or not performed. These results are consistent with the data of Yin et al. The total savings overall was AU$3 453, approximately 14% of overall observed cost of AU$ 3 849 for both hospitals combined. Limitations included use of electronic medical records and patients’ progress notes, and documentation issues relating to Wells score and CTPA orders. Patients who may have had falsely high D-dimer results due to variables like renal failure, sepsis or age were not excluded – they were recorded as used by the treating physicians. The sample size for cases at both hospitals was comparable to other studies.

Cost estimates for potential savings provide some insight into how simple improvements in clinical practice can affect the cost-effectiveness of investigation strategies.

Table 1 Observed and standard protocol intervention cost analysis for the cohort of 436 patients set out by high-risk (227) and low-risk group (209) (A), observed and standard protocol cost for pulmonary embolism (PE) diagnosed in both groups with sensitivity analysis (B)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Standard protocol</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>CTPA</td>
<td>227</td>
<td>227</td>
</tr>
<tr>
<td>Cost D-dimer</td>
<td>$3413</td>
<td>$8532</td>
</tr>
<tr>
<td>Cost of CTPA</td>
<td>$115 770</td>
<td>$115 770</td>
</tr>
<tr>
<td>Totals</td>
<td>$119 183</td>
<td>$115 770</td>
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</tbody>
</table>

(B)

<table>
<thead>
<tr>
<th>Cost in AU$</th>
<th>n = 436</th>
<th>Sensitivity analysis</th>
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</thead>
<tbody>
<tr>
<td>Total observed (o)</td>
<td>$234 304</td>
<td>$233 348</td>
</tr>
<tr>
<td>Total standard protocol (SP)</td>
<td>$201 850</td>
<td>$192 160</td>
</tr>
<tr>
<td>Difference O-SP</td>
<td>$32 454</td>
<td>$41 188</td>
</tr>
<tr>
<td>Difference as % observed</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>O cost per PE diagnosed</td>
<td>$5449</td>
<td>$5427</td>
</tr>
<tr>
<td>SP cost per PE diagnosed</td>
<td>$4694</td>
<td>$4469</td>
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CTPA, computed tomography pulmonary angiogram.
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The genomic potential of the Aspirin in Reducing Events in the Elderly and Statins in Reducing Events in the Elderly studies

Paul Lacaze, Robyn Woods, Sophia Zoungas and John McNeil, on behalf of the ASPREE Investigator Group, ASPREE Healthy Ageing Biobank and the STAREE Investigator Group

Key words
- genomics, public health, epidemiology, biobank.

Abstract
Human genetic studies are continuing to increase in size and scale, but the availability of well-phenotyped longitudinal cohorts remains rare. Significant infrastructure, investment and effort are required to establish and maintain high-quality cohorts with biobanking, genetic consent and repeated clinical data measurements. Australia currently has two such cohorts established by Monash University as part of community-based clinical trials in the elderly. Both studies involve capture of demographic, mood, cognitive, physical performance, physical function, neuroimaging, audiometry and various clinical data types over an average of 5 years. The ASPirin in Reducing Events in the Elderly (ASPREE) cohort is comprised of 16 703 Australians aged over 70 years and 2411 Americans aged over 65 years – recruited and randomised to either daily low-dose aspirin or placebo to examine the preventative benefit of aspirin on a range of clinical outcomes. The STAtins in Reducing Events in the Elderly (STAREE) study uses a similar model, and is currently recruiting 10 000 men and women aged over 70 years across Australia randomised to either low-dose statins or placebo. Both cohorts involve biobanking and consent for genetic research, with recruitment through a network of general practitioners in the community. A combination of whole-genome and targeted

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1 STAREE members include PI and Chair Professor Sophia Zoungas, Professor John McNeil, Professor Andrew Tonkin, Professor Rory Wolfe, Professor Christopher Reid, Professor Mark Nelson, Professor Elsdon Storey, Professor Lawrie Bellin, Professor Walter Abhayaratna, Dr Stephanie Ward, Professor Neil Pouler, Professor Anthony Wierzbicki and Professor Robyn Langham.

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Conflict of interest: None.
Genomics, the study of DNA and genomes, has already led to major advances in the areas of cancer medicine, rare disease\textsuperscript{2} and infectious disease\textsuperscript{3}; however, whether it will have comparable impact for the prevention of common, chronic conditions remains to be seen. Most known genetic risk factors for common diseases infer only minimal risk based on current models,\textsuperscript{4,5} bringing into question whether genomic risk will add value over traditional risk factors for common, polygenic diseases, such as cardiovascular disease, diabetes, autoimmune disease and late-onset cancers.\textsuperscript{6}

Genetic association studies for complex disease are trending towards increasing sample size to achieve more statistically significant associations,\textsuperscript{6,7} which can sometimes be carried out at the expense of quality phenotyping and longitudinal clinical data collection.\textsuperscript{8} Alternative study designs involving more in-depth clinical profiling may help improve our understanding of gene–phenotype relationships for diseases where hundreds or thousands of genetic variants plus environment factors contribute to disease risk.\textsuperscript{6-10}

The resources required to conduct large-scale longitudinal cohort studies involving deep phenotyping are significant. They necessitate major investment and infrastructure in sample collection, storage, processing, data analysis, bioinformatics and linkage over many years\textsuperscript{11} and must ensure a consistently high standard of phenotypic and medical data collection. Such cohorts are generally established for epidemiology, rather than for genetics. However, if quality longitudinal studies can involve biobanking to enable genetic measures, they become particularly powerful resources for genetics, allowing the study of many different phenotypes and diseases together without ascertertainment bias.\textsuperscript{12-15}

Two significant cohort-based genomic resources are now becoming available in Australia to help provide valuable opportunities to study genetics alongside deep longitudinal phenotyping data. The ASPrin in Reducing Events in the Elderly (ASPREE) study\textsuperscript{16} is a large clinical trial conducted in general medical practices throughout Australia involving high-quality medical data collection accompanied by sample biobanking and consent for genetic analyses. ASPREE is a study of health outcomes in 16 703 Australians aged over 70 years and 2411 Americans aged over 65 years (including in ‘US minorities’) to examine the potential primary prevention benefits of low-dose aspirin in older healthy individuals. ASPREE also acts as a broader epidemiological study of healthy ageing.\textsuperscript{16}

ASPREE participants’ health is tracked longitudinally over an average of 5 (and up to 7) years capturing detailed clinical events as well as demographic, lifestyle, cognitive, physical function and neuroimaging data. The primary study endpoint is a composite of death, dementia or persistent physical disability with secondary endpoints, including cardiovascular and cerebrovascular disease, stroke, cancer, depression and clinically significant bleeding. All clinical events and dementia are adjudicated by expert committees, ensuring a particularly high standard of phenotypic data quality, and rare clinical research potential not usually seen in genetics and healthy ageing research.

The ASPREE Healthy Ageing biobank is a biorepository of blood, saliva and urine samples collected from more than 13500 ASPREE study participants who consented for medical and genetic research. In addition to these baseline samples, 3-year follow-up blood samples will be collected from 75 to 80% of biobank participants for longitudinal biomarker studies. The sample resource will allow molecular data to be integrated into Australia’s largest clinical trial.

The STAREE study is a related study of healthy ageing which is a randomised controlled trial of a statin involving 10 000 men and women over 70 years of age also conducted in general medical practices across Australia. The objective of the STAREE study is to determine the effect of statin therapy (40 mg atorvastatin) versus placebo, over an average 5-year treatment period, for the prevention of major cardiovascular events as well as mortality, disability and dementia. STAREE also involves collection of biospecimens and consent for genetic studies, including RNA collection for gene expression analysis.

Together, the ASPREE and STAREE studies will provide the rare opportunity to combine high-quality medical record data with genetic data on large numbers of older Australians, many of whom are still in good health beyond their 70s. This will allow research by Australian and US investigators into genetic risk factors for diseases of ageing, including dementia, cancer, stroke, diabetes and cardiovascular disease. The research can be conducted in a controlled longitudinal research setting where all personal data and results will be de-identified. Genetic data can also be used for the pharmacogenomic analysis of aspirin, statins and other drugs to identify...
potential biomarkers for drug efficacy and/or adverse reactions within the elderly. The study will also facilitate research into the genetics of healthy ageing and disease resilience by studying those who remain free of disease to an advanced age, even despite possibly carrying what are thought to be pathogenic mutations.17

The ASPREE and STAREE studies have the potential to become significant resources for public health research internationally, and help drive the field of genetic epidemiology forward to deliver translational impact to address the growing public health challenge of an ageing population. In particular they will offer an unusual opportunity to make genetic measurements on thousands of otherwise healthy individuals, making studies into gene penetrance, genetic resilience and healthy ageing possible.

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An audit of patients with mature T-cell non-Hodgkin lymphoma by transplant status in Tasmania

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Key words

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Abstract
This retrospective audit of patients diagnosed with mature T-cell lymphoma across a 10-year period provides contemporary information on the outcomes and treatment patterns of an Australian cohort. Forty-two patients diagnosed with mature T-cell lymphoma were identified from the Tasmanian Cancer Registry and analysed using medical records and simple statistical analysis. The demographics and outcomes of patients in this cohort were comparable to large international studies with treatment patterns in line with the best available evidence.

Mature T-cell non-Hodgkin lymphomas (NHL) are a heterogeneous group of diseases that are associated with poor outcomes due to the limited efficacy of available therapeutics. They are rare neoplasms that are estimated to comprise just 5–10% of lymphoid malignancies1 in Western centres, with the larger numbers of patients seen in Asia highlighting the geographic variation in this disease. Mature T-cell NHL generally displays an aggressive clinical course and accounts for up to 20% of aggressive lymphomas, despite their comparatively low incidence.1

In broad terms, mature T-cell NHL can be subdivided into nodal, extranodal and cutaneous forms; however, the disease is far more diverse and actually encompasses 23 separate entities.1–3 Each entity is clinically, immunologically and morphologically distinct from each other and also, the more common primary cutaneous (CD30-positive) T-cell lymphomas. The most common mature T-cell NHL include peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), angioimmunoblastic, enteropathy-associated and cutaneous T-cell lymphomas (mycosis fungoides and Sezary syndrome); each with variable incidence and treatment patterns.1

In the absence of large randomised controlled trials, the management of mature T-cell lymphomas is presently based upon retrospective research. In 2014, the Italian Society of Hematology (and other affiliated societies) published guidelines for the management of adult T- and natural killer-cell lymphomas, which were based on the best available evidence.2 In general, the guidelines advocate for the use of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)-based chemotherapy, followed by autologous haematopoietic stem cell transplant (ASCT) consolidation, or alternatively, at first relapse for eligible patients. This treatment paradigm has largely been adopted internationally as the ‘standard of care’ unless a clinical trial is available.3 Despite this, long-term disease-free survival occurs in only 10–30% of cases.4

At present, there is a paucity of data available on the outcomes of Australian patients diagnosed with PTCL and this retrospective audit of the Tasmanian population contributes to our current understanding of the condition in the Australian setting. We report the outcomes of patients diagnosed with mature T-cell NHL in Tasmania between 2003 and 2013 managed with varying treatment patterns, including high-dose therapy and ASCT.

Ethics approval was granted following application to the Human Research Ethics (Tasmania) Committee. All adult patients with a diagnosis of a mature T-cell NHL between January 2003 and December 2013 were identified using the Tasmanian Cancer Registry (TCR). Demographic information and date of death were obtained from the TCR. Diagnostic and treatment information,
Table 1  Patient characteristics, lymphoma subtypes and induction chemotherapy details

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall median age at diagnosis (years)</td>
<td>67 (range 47–89)</td>
</tr>
<tr>
<td>Median age at diagnosis for patients receiving ASCT (years)</td>
<td>62 (range 47–68)</td>
</tr>
<tr>
<td>Median age at diagnosis for patients not receiving ASCT (years)</td>
<td>71 (range 54–89)</td>
</tr>
<tr>
<td>Male</td>
<td>16 (55)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Types of mature T-cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>12 (41)</td>
</tr>
<tr>
<td>Enteropathy-associated</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Angioimmunoblastic</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Extramedal</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Induction chemotherapy details</td>
<td></td>
</tr>
<tr>
<td>CHOP</td>
<td>16 (55)</td>
</tr>
<tr>
<td>CHOEP</td>
<td>1 (3)</td>
</tr>
<tr>
<td>CEOP</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (7)</td>
</tr>
<tr>
<td>None</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

ASCT, autologous haematopoietic stem cell transplant; CEOP, cyclophosphamide, etoposide, vincristine, prednisolone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

and date of last follow up were then extracted from the medical record. The minimum follow-up period was 19 months from diagnosis. Simple descriptive statistical analysis of patient characteristics and survival was performed.

All 42 patients identified by the TCR were reviewed for inclusion in this study. Thirteen patients were subsequently excluded due to an incongruent diagnosis in medical records or pathology reports (11 patients, 26%) or because their records were unable to be accessed (2 patients, 5%). The remaining 29 patients were included in the analysis. Demographic information and pathological diagnoses are detailed in Table 1.

Twenty-seven patients (93%) received upfront chemotherapy with the remaining two not receiving chemotherapy due to poor performance status at diagnosis (7%). Sixteen patients (55%) received CHOP chemotherapy and 20 patients (69%) received a CHOP-based regimen (Table 1). Five patients (17%) went on to receive further chemotherapy as part of their induction. Twenty-one patients (78%) achieved a complete or partial response following induction chemotherapy; and the remaining six patients had no response (11%), progressive disease (4%) or an unknown outcome (7%). Eight patients (31%) subsequently received ASCT; five (63%) upfront and three (37%) at first relapse. ASCT was performed for all subtypes excluding extranodal T-cell lymphoma. All patients received BEAM conditioning (carmustine, etoposide, cytarabine, melphalan). The median timing of transplant was 9 (range 6–27) months from time of diagnosis and there was no transplant-related mortality.

The overall median survival of patients in this cohort was 17 (range 0–43) months from diagnosis with a median follow up of 20 (range 0–108) months (up until 31 July 2015). Overall mortality was 69% during this period. When analysed by transplant status, median survival was 26 (range 16–43) months in the ASCT group and 13 (range 0–24) months in the non-ASCT group. The overall 1-year and 2-year survivals following diagnosis were 73 and 34% respectively. The median follow-up of the surviving subjects was 47 (range 21–108) months. All recorded deaths were related to disease progression (Fig. 1).

This study has provided valuable information on the outcomes for patients diagnosed with a mature T-cell neoplasm in Australia. The relative incidence of mature T-cell NHL subtypes observed was mostly similar to large international studies, such as the International T-Cell Lymphoma Project. While PTCL-NOS was the most common subtype in both studies (40% in this study versus 25.9% in the International T-Cell Lymphoma Project), the incidence of less common mature T-cell NHL was more variable. It is difficult to compare directly the two studies, however, due to the inclusion of some T-cell and natural killer cell NHL subtypes in the International T-Cell Lymphoma Project, which were not included in our study. Despite this observation, the apparent variation in incidence may be attributable to the small numbers of patients eligible for inclusion in the study. The majority of patients included in our study were also treated in line with the best available evidence, including almost 70% of patients receiving a CHOP-based induction chemotherapy regimen. The median age of this cohort was 67 years and only three patients were younger than 60 years at diagnosis. This likely explains the relatively low use of intensified regimens, such as CHOEP (CHOP + etoposide), particularly given the addition of etoposide has only more recently been demonstrated to confer benefit for patients younger than 60 years. Nevertheless, overall outcomes were not significantly worse than expected in the cohort. Notably, none of our patients was enrolled on to a clinical trial in the frontline setting due to lack of trial availability. Since conclusion of this audit, a regular multidisciplinary lymphoma meeting has been introduced at our centre.

While poor when compared to other lymphoid neoplasms, the median survival of this cohort of mature
T-cell NHL is similar to other published reviews.\(^1,2\) There were several long-term survivors in both the transplant and non-transplant group, with median survival being longer in the transplant cohort. While direct comparison of survival in the ASCT and non-ASCT groups is not valid due to inherent selection bias, including younger age and likely better performance status and small patient numbers, our findings lend support to the role of high-dose therapy/ASCT for eligible patients with mature T-cell lymphoma given poor outcomes with conventional chemotherapy.

As approximately 25% of cases in the registry were not mature T-cell NHL, our study also highlights the limitations of registry data for the study of rare neoplasms, such as peripheral T-cell lymphomas and affirms the value of establishing prospective registries. In order to improve outcomes for this group of patients, international collaboration will be needed to increase clinical trial participation.

References


Figure 1: Kaplan-Meier survival probability 0–24 months from diagnosis. (\(\square\)) Overall; (\(\square\)), no autologous haematopoietic stem cell transplant (ASCT); (\(\square\)), ASCT.
LETTERS TO THE EDITOR

Clinical-scientific notes

Pantoprazole-induced hypomagnesaemia causing cerebellar syndrome and seizures

Proton pump inhibitors (PPI) are widely used in the treatment of gastro-oesophageal reflux and other related conditions. They are considered as very safe drugs. However, widespread and protracted use has led to recognition of some rare side-effects, such as hypomagnesaemia.1

Magnesium is an intracellular cation, necessary for a number of cellular enzymatic reactions. Hypomagnesaemia has been associated with a wide range of cardiovascular and neurological clinical presentations.

We describe a case of a recurrent cerebellar syndrome with seizures, which we attributed to hypomagnesaemia secondary to pantoprazole.

A 73-year-old woman presented to the emergency department having been found in a confused state at home. This was on a background of recent symptoms of nausea, dizziness, lethargy, anorexia and weight loss, of unclear aetiology. Her past medical history included gastro-oesophageal reflux, type 2 diabetes mellitus, hypercholesterolaemia, hypertension and depression. She had been taking 40 mg of pantoprazole daily for several years. Her other usual medications were prochlorperazine, candesartan, amlodipine, atorvastatin and metformin. There was no history of diuretic use. She was a non-smoker and did not drink alcohol to excess.

Shortly after arrival to hospital, she had two brief generalised tonic–clonic seizures, followed by post-ictal drowsiness. Electrocardiogram (ECG) showed rapid atrial fibrillation at 120 beats per minute. She had mild hypokalaemia (3.4 mmol/L), hypocalcaemia (1.95 mmol/L) and moderate hypomagnesaemia (0.38 mmol/L). She was transferred to the intensive care unit for supportive management and electrolyte replacement.

Her conscious state had improved 24 h after electrolyte replacement. Neurological examination at this time revealed evidence of a pan-cerebellar syndrome, with dysarthria, horizontal nystagmus on horizontal gaze, vertical and rotatory nystagmus on upward gaze, diplopia on horizontal gaze to both sides, bilateral finger-nose and heel-shin dysmetria and gait ataxia. Non-contrast computed tomography and magnetic resonance imaging (MRI) scans of the brain, electroencephalogram and cerebrospinal fluid examination were unremarkable.

Computed tomography scans of the chest, abdomen and pelvis showed no evidence of a malignancy, and anti-neuronal, anti-glutamic acid decarboxylase, anti-transglutaminase and anti-gliadin antibodies were negative.

Twenty days after admission, her symptoms returned and she had a further tonic–clonic seizure. Blood tests showed undetectably low serum magnesium (<0.1 mmol/L) and an ECG showed atrial fibrillation. She was again treated with intravenous electrolyte replacement.

Figure 1 Clinical events related to serum magnesium and calcium. AF, atrial fibrillation; IV, intravenous. (→), Ca; (——), Mg.
It was difficult to maintain normal serum magnesium levels despite repeated intravenous magnesium infusions (Fig. 1). Investigation revealed no evidence of renal magnesium wasting and there were no clinical pointers to excess gastrointestinal magnesium loss. Pantoprazole was suspected as causing the recurrent hypomagnesaemia and was ceased. One week after cessation, her magnesium levels stabilised at 0.8–1.0 mmol/L and did not further decline (Fig. 1). She has remained well subsequently.

This case is noteworthy in a number of respects. There are several previous reports of a subacute cerebellar syndrome occurring in association with hypomagnesaemia. However, those cases were associated with cerebellar hyperintensities on MRI, which were absent in this case. Furthermore, ours is the first reported case of cerebellar syndrome occurring as a result of PPI-induced hypomagnesaemia. The neurological manifestations of PPI-induced hypomagnesaemia in previous cases have been limited to seizures.

PPI are believed to cause hypomagnesaemia by inhibition of the transient receptor potential melatin 6 and 7 channels, thereby impairing gastrointestinal magnesium absorption. The mechanism of cerebellar dysfunction in hypomagnesaemia is unclear. As magnesium is an essential co-factor in the conversion of thiamine into active diphosphate and triphosphate esters, functional thiamine deficiency may be contributory.

Vascular endothelial dysregulation induced by hypomagnesaemia is another postulated mechanism.

Given the widespread use of PPI, it is important that clinicians are aware of this uncommon, but potentially under-recognised, adverse effect of this class of medications. We encourage clinicians to check periodically magnesium levels in patients on long-term therapy with PPI, and to consider PPI as a potential cause of unexplained hypomagnesaemia, and of neurological symptoms in hypomagnesaemic patients.

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References

Double fire tachycardia induced cardiomyopathy: first ever reported case in Australia

This is an interesting case of tachycardia-induced cardiomyopathy from a rare arrhythmia called double fire tachycardia or dual atrioventricular nodal non-reentrant tachycardia.

A 58-year old man was admitted with a 3-month history of worsening shortness of breath, orthopnoea and paroxysmal nocturnal dyspnoea. He denied chest pains, palpitations or pre-syncpe. Past medical history included paroxysmal atrial fibrillation (AF) and dyslipidaemia. His medications included aspirin, rosuvastatin and atenolol. Vitals were unremarkable except for a regularly irregular pulse at 148 beats/min. Examination revealed an elevated jugular venous pressure and bilateral basal crepitations.

B-type natriuretic peptide levels were 672 ng/L (normal <100 ng/L) while electrolytes and thyroid function tests were within normal limits. The electrocardiogram (ECG) pattern was consistent with dual atrioventricular nodal non-reentrant tachycardia (DAVNNT), also known as double fire tachycardia (Fig. 1A). There are dual ventricular responses with two QRS complexes per
single atrial impulse (P wave) with spontaneous transition from 1:2 DAVNNT to 1:1 AV conduction due to presumed fluctuation in autonomic tone. Transthoracic echocardiography showed a severely dilated and impaired left ventricle (LVEF 27%), mildly dilated right ventricle with moderate systolic dysfunction, and moderate mitral regurgitation. A myocardial perfusion scan excluded inducible ischaemia.

On electrophysiology study, the patient was found to be in sinus rhythm with two sequential His-ventricular electrograms per atrial electrogram (A-H1-V1-H2-V2 – Fig. 1B). No provocation with isoprenaline was required. Baseline programmed stimulation was not performed as the patient was in incessant ‘double fire’ during the study. Slow pathway (SP) radiofrequency ablation (RFA) was performed, with each subsequent sinus beat resulting in only a single ventricular electrogram and thus normalisation of the ECG (Fig. 1C). Retrospective review of prior ECG revealed DAVNNT in all cases; these had been misdiagnosed as AF. Follow-up echocardiography revealed improvement in LVEF to 50%.

Typical AV nodal re-entrant tachycardia (AVNRT) comprises a circuit with antegrade and retrograde conduction through the slow and fast pathways respectively. Dual antegrade conduction via both pathways may cause two ventricular depolarisations with ECG demonstrating a single P wave followed by two QRS complexes. This occurs rarely as it requires the absence of retrograde concealment into the SP. First described by Wu et al. in 1975,1 DAVNNT has rarely been recognised with fewer than 100 cases reported worldwide.2 It is mistaken for AF in 32%, or premature atrial complexes in 24% of patients.3 To our knowledge, this is the first reported case of tachycardia mediated cardiomyopathy due to DAVNNT in Australia.

The differential diagnosis of a narrow-complex tachycardia with a P:R ratio of 1:2 includes DAVNNT junctional bigeminy and all the subnodal supraventricular tachycardias (SVT) in association with 2:1 retrograde or upper common pathway block including AVNRT, junctional tachycardia, re-entrant tachycardia with a concealed nodofascicular/nodovenous pathway or intranodal reentry.4 In our case, the sinus P wave morphology excludes all subnodal SVT and the persistence of ‘double fire’ across different sinus rates makes junctional bigeminy unlikely.

Recognition of this ECG pattern and its distinction from AF is critical in order to avoid unnecessary therapies (anticoagulation) and complications (cardiomyopathy). Case reports suggest DAVNNT is resistant to medical therapy.5 SP RFA is safe, efficacious and curative.

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Plug-assisted retrograde transvenous obliteration of splenorenal shunts for refractory hepatic encephalopathy

A 63-year-old Caucasian woman presented to hospital with confusion and decreased level of consciousness, on a background of Child’s Pugh B cirrhosis secondary to non-alcoholic steatohepatitis. She was diagnosed with hepatic encephalopathy (HE) and managed with standard medical therapy of lactulose and rifaximin.

Despite prophylactic medical therapy, the patient had five further admissions with West Haven Grades II–III HE between October 2014 and July 2015. No precipitant was identified for these episodes and the patient showed significant cognitive and functional decline over this period.

Investigations for the precipitant of HE included a computed tomography of abdomen which demonstrated portal hypertension with gastro-oesophageal varices and a large splenorenal shunt (Fig. 1). Endoscopy showed grade one oesophageal varices which did not warrant prophylactic therapy.

In view of her refractory HE, the patient was consented and worked up for plug-assisted retrograde transvenous obliteration (PARTO) of her splenorenal shunt. Access was obtained through the right femoral vein. Digital subtraction angiography of the shunt demonstrated a high flow varix with partial drainage through inferior phrenic veins. These outflow vessels were embolised with coils to prevent non-target treatment (Fig. 2).

The dominant varix was too large for the available 14 mm balloon occlusion catheter and was embolised with tandem Amplatzer Plug (Plymouth, MN, USA) and sclerosant slurry (4% sodium tetradecyl sulphate, gel foam and Lipiodol) (Fig. 3). On completion venogram, an additional previously unvisualised varix outflow was seen. Given the prolonged procedure time, radiation and contrast dose, a decision was made to terminate the procedure and re-evaluate the necessity of occluding the residual varix.

Reference:
As the patient’s encephalopathy improved post-procedure, it was decided not to pursue obliteration of the residual varix. The patient has not had recurrence of encephalopathy in 12 months.

Balloon-occluded retrograde transvenous obliteration was described by Kanagawa in 1991. It is an effective treatment to obliterate portosystemic shunts, resulting in increased portal blood flow. In PARTO, a vascular plug is used as a substitute for the balloon and this has been found to be technically and clinically equivalent. PARTO decreases procedure time and risk of potential complications as an indwelling balloon catheter is not required.

HE is a major complication of cirrhosis which affects up to 30–40% of patients. Overt HE is a poor prognostic factor and HE patients requiring hospitalisation have 1-year survival rates of less than 50%. There is significant morbidity associated with repeated admissions and poor quality of life. Studies have indicated that up to 46–70% of patients with refractory HE have large spontaneous portosystemic shunts. The clinical improvement in HE post shunt embolisation is sustained for up to 2 years and can provide significant benefits to quality of life.

Our case suggests that partial obliteration of a splenorenal shunt can be beneficial in improving refractory encephalopathy. PARTO is a minimally invasive and effective treatment that can be used to target these shunts. Portosystemic shunts should be looked for in patients with HE and closure of shunts should be considered in patients who are refractory to medical therapy.

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References

General correspondence

An appeal to the medical community: the need for laboratory specialist input in the development of clinical practice guidelines

Many clinical practice guidelines involve laboratory testing. The majority of laboratory errors are not analytical (within the control of the laboratory) but inappropriate choice of tests and inappropriate interpretation and utilisation of laboratory results.1–4 In 2013, the European Federation of Clinical Chemistry and Laboratory Medicine and European Union of Medical Specialists Joint Working Group on Guidelines proposed a checklist of issues that should be addressed in all clinical practice guidelines when laboratory testing is recommended.5 The issues include indications for using the test, clinical performance of the test, sampling procedures, test methodology, analytical and biological interferences, test quality issues and test interpretation. They also proposed the involvement of a laboratory specialist in the guideline development process. Their aim was that correct information relating to a laboratory test provided in the guideline might reduce diagnostic errors.

Three years on, we feel compelled to appeal to the medical community the need for laboratory medicine specialist input in the development of clinical practice guidelines. The updated Endocrine Society Clinical Practice Guideline on primary aldosteronism (PA) in 2016 includes a list of cut-offs for the screening and confirmation of PA.6 However, some of the cut-offs derived from older laboratory assays such as radioimmunoassays may no longer be relevant in the current era of automated immunoassays.7 In a clinical biochemistry journal, Denimal and Duvillard8 highlighted two recent studies evaluating the plasma aldosterone-to-renin ratio (ARR) with automated chemiluminescent immunoassays. In a study by Manolopoulou et al.,9 an ARR cut-off of 1.12 ng/dL/mIU/L had 99% sensitivity and 79% specificity for PA diagnosis. In another study by Burrello et al.,7 an ARR of 2.7 ng/dL/mIU/L had 78% sensitivity and 100% specificity for PA diagnosis. Therefore, the application of a corresponding cut-off of 3.7 ng/dL/mIU/L based on an older assay proposed in the PA guideline5 may lead to false-negative classification of patients.3 The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for acute kidney injury (AKI) recommends serum creatinine-based criteria for the diagnosis and staging of AKI.8 However, minimal attention was paid to the analytical aspects of creatinine measurement. One of the AKI criteria is an increase in serum creatinine by ≥26.5 μmol/L within 48 h.8 A coefficient of variation (CV%) of 4% has been suggested by laboratory experts to be the maximum tolerable imprecision to identify reliably an increase in serum creatinine of 26.5 μmol/L with certainty.5 However, in a recent study evaluating the current status of creatinine assays (Jaffe-based and enzymatic), all Jaffe creatinine methods (still widely used by clinical laboratories) exceeded the proposed clinically acceptable limit at creatinine <100 μmol/L, whereas all enzymatic methods achieved a CV <4% across the studied analytical range of 80–239 μmol/L.9 Therefore, to recommend strict serum creatinine-based criteria for the diagnosis of AKI (e.g. an increase in serum creatinine by ≥26.5 μmol/L) without considering creatinine assay imprecision is potentially misleading. On the other hand, it is heartening that the KDIGO Clinical Practice Guideline for chronic kidney disease working group comprising a laboratory specialist addressed the analytical aspects of creatinine measurement. They discussed potential endogenous and exogenous interferences with creatinine assays (which we feel are rarely considered by clinicians) and acknowledged the imprecision of estimated glomerular filtration rate at high levels due to assay variation at low serum creatinine concentrations.10 Laboratory assays continue to evolve. For quality laboratory testing and good patient care, a closer cooperation between medical specialists and laboratory specialists is essential.1,11

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Variation in dispensing of opioid analgesics in Australia

Islam and colleagues have documented important and concerning trends in dispensing of opioids in Australia. In their article, they lament the lack of data on regional variation in information for opioid dispensing. We draw attention to the recently published Australian Atlas of Healthcare Variation which maps geographical variation in opioid dispensing across Australia at Statistical Area 3 level by place of residence and provides the data by state and territory, socio-economic status and remoteness. The online interactive version of the atlas also maps by primary Health Network and Local Health Network. In 2013–2014, nearly 14 million prescriptions were dispensed through the Pharmaceutical Benefits Scheme for opioids. The number of prescriptions dispensed was more than 10 times higher in the area with the highest rate (Central Highlands, Tasmania) compared with the area with the lowest rate (Daly–Tiwi–West Arnhem, Northern Territory). However, even when the areas with the lowest and highest rates were excluded considerable variation was still seen in dispensing (2.9 times more in the areas with the highest rates than in the areas with lowest rates).

There may be a range of reasons for the geographic variation in opioid dispensing. Lack of access to multidisciplinary pain treatments and specialist pain medicine physicians especially in rural and regional areas may be a factor. Differences in medical knowledge and training may contribute. In addition socio-economic-cultural factors may play a role as the authors suggest. However, the extent of geographic clinical variation is unlikely to be explained entirely by patient condition or need. The variation is likely due in part to treatment preference of the prescriber and lack of access to more evidence based therapies.

Islam and colleagues predict a continued increase in opioid prescribing/dispensing in Australia as the population ages, largely due to the use of opioids for treatment of chronic non-cancer pain (CNCP) and as the burden of cancer increases. However, it should be noted that there is a lack of evidence to support the effectiveness and safety of opioids for treatment of CNCP with the weight of evidence supporting multidisciplinary self-management approaches. Various professional groups in Australia are now speaking more strongly against the use of opioids for CNCP. The National Prescribing Service suggests the doctor ‘consider deprescribing at every visit’ in the context of opioid prescription for CNCP. The Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists state that ‘opioid pharmacotherapy cannot be considered to be a core component of the management of CNCP’. The lack of scientific evidence supporting use of opioids in CNCP and the changing views of professional organisations may mitigate against the further rise in opioid prescribing predicted by Islam and colleagues.

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Letters to the Editor

References


Cultural competence and over-investigation

We propose a simple explanation for the conclusions raised in the study by Liao et al.1 To us, it highlights the issue of cultural competence. This is an area that requires further attention and the Royal Australasian College of Physicians (RACP) has built this into its curriculum.

The paper1 itself showed that patients with European heritage had higher positive rates than non-Europeans for computed tomography pulmonary angiography (CTPA) and lower ultrasound scans (USS). The statistics presented are very compelling, with strong statistical differences identified between European and non-European patient groups for rates of positivity for CTPA and lower limb USS in this regard.

A simple explanation for the significant differences in positivity rates for the investigations (as reiterated in figures 2 and 4 by Liao et al.1) is over-investigation of non-Caucasian patients. Simply, non-Caucasians cannot communicate adequately to the treating doctor the nature of their chest pain or leg pain. This may be due to language or cultural differences (or a combination of the two). They might not be able to describe their symptoms adequately. They might just nod yes in response to everything that the doctor says. In desperation, the treating doctor requests further – and sometimes unnecessary – imaging and/or other investigations. In fact, the resulting over-imaging – and its consequences – was discussed by Liao et al.1 Higher positive rates for CTPA and leg USS was found in ‘European’ patients – this might actually, in fact, reflect lower rates in non-Europeans because positives were diluted by cases of over-investigation. It is known that diagnosis can be biased by altered linguistic cues.2

In fact, the terms ‘European’ and ‘non-European’ might not address the core of the issue. This is more about whether the patient–doctor communication is adequate. The European/non-European division is too simplistic. Some Europeans speak little English – and cannot be adequately understood by the doctor. The non-European group is very heterogeneous – including people from various Asian, African, South American and Oceanic countries and so on. Doctors have to recognise the communication barriers, otherwise they will be prisoners to the ‘more investigations’ reflex. Doctors – especially highly qualified ones – should be better than that.

Intuitively, we know that all beings are a manifestation of a combination of ‘nature’ and ‘nurture’. A more sophisticated way of saying this: phenotypes reflect a combination of genetics and environment. In this instance, we propose that environmental factors are far stronger contributors than any sinister underlying genetic mechanism. The issue, in our mind, is that diagnosis is hindered by lack of cultural competence by doctors and we are glad that the RACP has designated this as one of the key components of its educational priorities.3

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References


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**Corrigendum**

The authors would like to draw the readers’ attention to an error in the following article:


Figure 3 and its legend are incorrect. The correct figure and its legend are reproduced below:

![Figure 3](image-url)  
*Figure 3* Standardised UK mortality rate data of diseases of various systems of the body. Whilst the mortality of most diseases is gradually declining over time, mortality because of liver disease is increasing at a significant rate. Data were normalised to 100% in 1970, and subsequent trends were plotted using the software Statistical Package for the Social Sciences. Data are from the WHO-HFA database. (---), Liver; (——), endocrine or metabolic; (—), diabetes; (—), neoplasms; (—), ischaemic heart disease; (—), circulatory; (—), cerebrovascular; (—), respiratory. Reproduced from Williams *et al.*,10 with permission.

The authors apologise for the error.

**Reference**

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