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EDITORIAL

Foregoing low-value care: how much evidence is needed to change beliefs?

It’s not always easy to let go of time-honoured practices which are shown to be ineffective or even harmful. A considerable literature has grown up around how to encourage clinicians to align their routine practice with robust scientific evidence. Much of this ‘implementation’ or ‘translation’ research has focused on explaining and overcoming underuse of effective interventions. The landmark CareTrack study of the quality of healthcare in Australia estimated that just over 40% of eligible patients do not receive evidence-based care. On the flip side, widespread use of ineffective interventions, which may consume up to 30% of healthcare budgets, has received much less attention at a time when healthcare systems are required, by fiscal constraints, to maximise health benefit for every dollar spent.

Clinicians are often reluctant to relinquish established clinical practices despite seemingly compelling evidence to do so. For example, US studies showed no decrease in the use of percutaneous coronary intervention (PCI) to reopen totally occluded infarct-related arteries beyond 24 h after acute myocardial infarction despite publication of a large trial showing no benefit and release of revised guidelines. Similar experience has been noted in regards to PCI use in patients with stable, non-critical coronary artery disease. In many hospitals, protocols decree that batteries of preoperative tests, routine replacement of intravenous cannulae every few days and daily chest X-rays on all intensive care patients be performed, irrespective of clinical need – despite considerable evidence that more selective, less costly manoeuvres are equally safe and effective. Futile, aggressive care delivered to patients with advanced end-stage disease or terminal illness diminishes dignity and quality of life while consuming resources. Potential waste and possible harm also occur when an intervention proven to be effective within a very specific population is inappropriately applied to a wider spectrum of patients for whom benefit has never been demonstrated (indication creep). More than one in five implantable cardioverter-defibrillators in the US are inserted for off-label indications for which benefit has not been evaluated.

To healthcare funders and policymakers, clinician resistance to foregoing interventions that robust evidence reveals are of no benefit, or even harmful, is perplexing, to say the least. The question they may well ask is: how much evidence do you need to change your mind?

Determinants of decision-making

Clinicians will rightly argue that evidence has to be compelling before they disown practices that have stood the test of time and, in their personal experience at least, appear safe and to have done some good. However, what constitutes ‘compelling’ evidence is very much in the eye of the beholder, although two themes predominate: epistemic factors around the trustworthiness of the research (objectivity, consistency, clinical plausibility and non-selective reporting of outcomes) and the likely benefit for individual patients (effect size, applicability of ‘average study patient’ treatment effects to specific subgroups or unselected real-world populations, time to effect, and value to patients of the outcomes measured). Still, the threshold of ‘compellingness’ that may serve as a ‘tipping point’ for a collective change in beliefs remains uncertain, at least in the medical world, and will likely differ from one clinical scenario to the next.

Moreover, research evidence is not the only determinant of clinical decision-making. Various cognitive and non-cognitive factors may explain the tendency towards unnecessary care, with many reflecting clinician desire to avoid potential injustice to individuals from withholding interventions that may possibly bestow some benefit (Table 1). However, while these factors are no doubt important, there are two more fundamental factors that may underpin resistance to change.

Cognitive dissonance

Cognitive dissonance is the inability to reconcile new evidence with highly ingrained prior beliefs that both determine and are reinforced by routinised practice – one believes so one does, and as one does, so one believes. Such beliefs are highly personal and internalised based on individual experience, interpretation of past research, exposure to the views of respected peers, and socialisation into the norms and traditions (or culture) of one’s chosen specialty. What we believe (and want to believe) is tightly bound to the central human need to belong to and seek comfort within, a group that shares similar values and
outlook. Challenging current professional paradigms runs the risk of being cast out and ostracised from the group. Pioneering medical thinkers from Ignaz Semmelweis (septic technique to prevent puerperal sepsis) to Barry Marshall (eradication of Helicobacter pylori to prevent recurrent peptic ulcer) have had to confront and overcome collective cognitive dissonance.

When research supports strongly held beliefs, clinicians more readily accept the conclusions – despite major methodological flaws – and use them to reinforce current practice11 or in some cases add to current practice, even if the evidence is far from definitive.14 In contrast, when research runs counter to strongly held beliefs, even multiple studies involving patients representative of everyday practice may not prove persuasive. All sorts of reasons, including flaws in study designs (both real and imagined) and limited applicability ‘to my patients’ may be cited to discredit the results.19 There are notable exceptions, chiefly reports that unequivocally show serious harm from commonly performed interventions, more so if patients get to know about it, raising the risk of medicolegal liability. There was an immediate reduction in the use of hormone replacement therapy in post-menopausal women20 and of prophylactic anti-arrhythmic agents following acute myocardial infarction,21 following trials showing increased risk of serious adverse events, information that was quickly disseminated in the lay press.

### Table 1 Biases towards unnecessary care

- Clinician regret at not administering a treatment when it may lead to benefit (regret of omission) overpowering regret for the consequences of an unnecessary treatment (regret of commission)
- Pro-intervention bias, especially among younger clinicians, towards choosing action over inaction even if marginal benefits of action are very small
- Pro-technology and ‘innovation’ bias towards too readily believing that newer treatments and technologies are superior to their predecessors
- Desire to please referring clinicians
- Fear of patient approbation or litigation for not doing things (defensive medicine)
- Supply-driven demand (desire of industry and providers to generate income in presence of excess capacity)
- Overestimation by both clinicians and patients of treatment benefits and safety
- Overreliance on pathophysiological or anatomical reasoning, or surrogate outcomes that do not necessarily translate into patient-important benefits
- Clinical practice guidelines lacking a sound evidence base or written by conflicted panelists
- Fee-for-service funding (which rewards quantity not quality of services)

### Professional autonomy and reactance

Clinicians value their autonomy and being perceived as sound arbiters of medical knowledge. Having to accept evidence that runs contrary to one’s beliefs and refutes what had been regarded as effective interventions can threaten one’s sense of competence, professionalism and freedom to choose. This may incite a state of psychological reactance, a tendency to resist perceived attempts by others – especially those outside one’s professional network – to control behaviour.22 Individuals can react in a way that affirms their ability to choose and often become more entrenched in their original beliefs. Once aroused, reactance may heighten sensitisation to additional threats to freedom of choice that further constrains the capacity for dispassionate debate. To date, psychological reactance of clinicians has been little studied in the medical literature with most reports pertaining to patient non-adherence with medical advice.23

### Implications for physician practice

Putting these cognitive biases to one side, there is no place for continued support of ineffective or harmful practices among clinical professions that base their practice and authority on good science. Recent investigations have disclosed more than 150 high-volume clinical services on the Medicare Benefits Schedule that are potentially of low-value, with almost half being ineffective or harmful on the basis of multiple trials and systematic reviews.8 Past experience in encouraging clinicians to align practice with best evidence suggest educational or awareness-raising strategies, clinical audits and feedback, academic detailing, and other professionally mediated interventions have limited impact in curtailing inappropriate care.1

Funders and policymakers increasingly view such activities as too slow and incremental. Consequently, they place greater faith in ‘forced function’ manoeuvres of which the first and foremost are financial incentives (or increasingly disincentives) in the belief that clinicians will no longer do things if they are not being paid, or paid as much, to do them. Value-based funding programmes and pay for performance schemes in the US and UK are seeking, rightly or wrongly, to reduce funding for publicly subsidised services deemed to be of no value and reallocate saved resources to higher value healthcare that confers greater benefit. So-called ‘bundled payment’ models, for example, provide clear disincentives for including low-value services in the bundle that attracts a set price for an entire care package. Other strategies include public reporting of quality standards for hospitals (and in the future possibly individual units and consultants) that include
overuse as well as underuse of care, restricting use of certain interventions to narrowly defined populations of eligible patients and highly competent providers in order to maximise benefit, and increased use of blocking systems that disallow the ordering or prescribing of selected tests or treatments. As stewards of tax-payer funds, Australian authorities will likely consider these approaches in the near future.

While interventions that are clearly of low value represent low-hanging fruit in any programme aimed at reducing waste, more challenging are interventions ‘at the margin’ where genuine uncertainty exists as to who will and will not benefit from them. It is in no one’s interest to reduce indiscriminately utilisation such that patients who clearly need specific interventions are denied them. If as clinicians, we wish to avoid being marginalised in debates around minimising use of ineffective or harmful interventions and reduce the risk of being governed by policy decree with its inherent clumsiness and potential for unintended consequences, we will have no choice but to define low-value care and answer the question ‘how much evidence is enough to change beliefs?’

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Vancomycin therapeutics and monitoring: a contemporary approach

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Abstract
Vancomycin remains a clinically useful antibiotic despite the advent of several alternative drugs. Optimising vancomycin therapy with therapeutic drug monitoring is widely recommended. The aim of therapeutic drug monitoring is to help the clinician to achieve target pharmacodynamic parameters in the case of vancomycin, an area under the concentration time curve/minimum inhibitory concentration ratio of \(\frac{AUC}{MIC}\) of \(\geq 400\). Vancomycin monitoring methods can be categorised into four categories: empiric trough concentrations; linear regression analysis (one-compartment model), population methods and Bayesian estimation procedures. Although the empiric trough concentrations and population methods are easy to use and require minimal resources, there are large differences in the published vancomycin model parameters. This demonstrates that there is great variance in pharmacokinetic parameters between the models and a single vancomycin model cannot be applied to all patient populations. The linear regression and Bayesian methods recommended more accurate dosage regimens; however, they require additional resources such as information technology and healthcare personnel with background training in pharmacokinetics. The Bayesian methods offered additional advantages such as calculation of doses based on a single-serum concentration and optimisation of the patient’s previous pharmacokinetic data to determine subsequent dosage regimens. Computerised programs, utilising the Bayesian estimation procedures, are able to achieve target concentrations in a greater percentage of patients earlier in the course of therapy than the empiric trough concentrations and population methods. We recommend the use of these programs providing there is appropriate expertise available to make appropriate recommendations.

Introduction
Vancomycin was first used in clinical practice in 1958. Since that time, the antibiotic achieved notoriety (including the nickname ‘Mississippi Mud’ because of the brown colour of impurities) and subsequently widespread use as the primary therapy for infections with methicillin-resistant Staphylococcus aureus (MRSA). In the present era, there are several other options available for the treatment of MRSA infections. Additionally, resistance of enterococci and staphylococci to vancomycin has emerged over the last two decades. In this context, we seek to discuss the relative efficacy of vancomycin compared with other therapies, the advent of resistance, dosing regimens of the drug, monitoring and toxicity.

Indications and efficacy
Vancomycin is only active against Gram-positive bacteria, with virtually no activity against Gram-negative bacteria, mycobacteria or fungi. Intravenous vancomycin is used for staphylococcal infections, especially when resistance to antistaphylococcal penicillins is suspected or proven.

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Conflict of interest: David Paterson has previously been on the advisory boards for Merck, Astra Zeneca, Johnson and Johnson, Novartis, and Pfizer.
vancomycin. Second, control of the infection source such as clindamycin or cotrimoxazole. May often be treated with alternatives to vancomycin, infected indwelling devices are also imperative. It should (e.g. surgical debridement) and prompt removal of infected indwelling devices are also imperative. It should also be noted that community-acquired MRSA infections may often be treated with alternatives to vancomycin, such as clindamycin or cotrimoxazole.

**Toxicity**

Many of the adverse events attributed to vancomycin in the past were probably attributable to impurities present in older preparations that were present until the mid-1980s. Apart from rare cases of interstitial nephritis, it remains controversial whether modern preparations of vancomycin cause nephrotoxicity. Studies have used inconsistent definitions and have had difficulty establishing the temporal relationship. They are also confounded by the use of other nephrotoxins, other potential causes of nephrotoxicity such as sepsis and underlying comorbidities. Several studies have shown an association between higher trough concentrations (>15 mg/L) and nephrotoxicity, but it is generally unclear whether vancomycin is the cause or merely an indicator of renal toxicity. Data are conflicting on whether vancomycin in combination with an aminoglycoside is more nephrotoxic than an aminoglycoside alone. A consensus approach is first to consider other causes (particularly concomitant nephrotoxins and sepsis-related organ dysfunction) and ensure adequate hydration before attributing nephrotoxicity to vancomycin.

Infusion-related reactions associated with vancomycin have been well described and referred to as the ‘red man’ syndrome. It is characterised by tingling or itch associated with flushing of the upper body. It usually occurs within a few minutes of the start of the infusion and resolves soon after cessation of the infusion. The risk of this reaction is generally minimised by limiting the infusion dose to a rate of 10 mg/min (around 1/2–2 h for most infusions). However, more rapid infusions are often administered as surgical prophylaxis where patients are closely monitored. In cases where signs persist after cessation of the infusion or hypotension is prominent, hypersensitivity should be considered.

Otoxicity appears to be an uncommon adverse event, and most reports relate to use of older preparations. Neutropenia may be more common than is generally appreciated with reports suggesting up to 12% of patients have neutropenia. This appears to be related to the duration of therapy, with the highest incidence in patients who receive >20 days of treatment.

**Resistance and treatment failure**

There are various categories used to describe vancomycin non-susceptibility in *S. aureus*; heteroresistant vancomycin intermediate *S. aureus* (hVISA), vancomycin intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) (Table 1). VRSA (minimum inhibitory concentration (MIC) ≥16 μg/mL) occurs rarely following acquisition of the *vanA* gene and is limited to a handful of cases with none documented in Australia. Although VISA (MIC 4–8 μg/mL) isolates are more frequent than VRSA, they are also uncommon. Several genetic mutations are associated with VISA isolates and differentiate VISA from vancomycin-susceptible *S. aureus* (VSSA). For example, sequential acquisition of mutations in the two-component regulatory systems vraSR and graRS was responsible for the VISA phenotype of the originally described VISA strain, Mu50. Single nucleotide polymorphisms in these and other VISA candidate loci (*vraSR*, *yqf*, *graRS*, *walRK* and *rpoB*) are present more frequently in VISA isolates compared with VSSA. The consistent phenotypic finding of VISA strains is increased cell wall thickness that results in resistance by preventing vancomycin diffusion to its active site. Most guidelines recommend alternative antibiotics for the treatment of VISA and VRSA infections.

hVISA is characterised by the presence of a vancomycin-resistant subpopulation and can be detected in up to 10% of Australian MRSA bloodstream isolates. However, unlike VISA, hVISA isolates test susceptible (MIC ≤2 μg/mL) by conventional methods and specialised laboratory testing such as population analysis profiling is required for detection. Concerns of clinical ‘resistance’ have emerged with several reports documenting increased mortality and treatment failure with hVISA and in infections caused by VSSA isolates that have MIC close to the breakpoint (MIC 2 μg/mL).

Definitions of treatment failure may include persistent symptoms or signs of infection, persistently positive cultures, relapsed or recurrent infection, and mortality.
Given the evolving understanding of the concepts of vancomycin resistance and non-susceptibility, further research is required to understand the relationship between vancomycin treatment, vancomycin MIC and outcome. Nevertheless, there are some practical considerations that may assist clinicians in predicting or avoiding treatment failure with vancomycin. Clinical factors such as advanced age, prior MRSA colonisation or infection, prior vancomycin exposure, high bacterial load infections (e.g. bacteraemia, endocarditis, osteomyelitis) and persistent bacteraemia have been associated with hVISA and vancomycin treatment failure. Therefore, laboratory testing of vancomycin MIC and for hVISA should be prioritised in patients with persistent bacteraemia and prior MRSA infection. If hVISA is identified and clinical failure is apparent, then consider an alternative agent.

It should also be noted that other factors may be implicated in apparent vancomycin treatment failure rather than failure of vancomycin itself (e.g. different bacterial genotypes or other host-pathogen factors). However, these developments are beyond the scope of this review.

### Alternatives to vancomycin for the treatment of MRSA

Several alternative antibiotics to vancomycin have been registered in recent years for the treatment of Gram-positive infections, including agents such as linezolid, daptomycin, ceftaroline and telavancin. A detailed discussion with respect to side-effects, advantages and disadvantages of the individual agents is beyond the scope of this review, and readers are referred to a recent publication for further details.

### Using vancomycin susceptibility testing to guide treatment

Vancomycin susceptibility and MIC can be measured using a variety of methods including agar-based and semiautomated systems. Results differ between methods especially when compared with the reference broth microdilution. Hence, the method used to obtain the MIC should be considered when MIC information is used to inform treatment decisions. In infections with risks for vancomycin treatment failure (as described earlier), it is recommended that vancomycin MIC and screening for hVISA be performed. Algorithms have been proposed to guide clinicians and laboratories with vancomycin susceptibility testing and interpretation.

When a patient has an infection where the MIC is near the resistance breakpoint (MIC 2 μg/mL, using the reference method), close assessment of treatment response is critical. Maximising pharmacodynamic parameters and attaining target therapeutic serum concentrations may improve vancomycin efficacy at these borderline MIC. Note that pharmacodynamic targets were derived using the MIC reference method, and the same targets may not be applicable with other MIC methodologies. While it is clear that vancomycin should be avoided in VISA and VRSA, infections caused by these strains are infrequent. The significance of hVISA remains controversial and subject to debate; as such, published recommendations continue to recommend vancomycin. However, if there are persistent symptoms or signs of infection despite optimising treatment with vancomycin, then consideration of an alternative antimicrobial is warranted.

---

**Table 1** Differing terminology used in reporting *Staphylococcus aureus* resistance by region

<table>
<thead>
<tr>
<th>S. aureus vancomycin MIC (μg/mL)</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
</tr>
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<tbody>
<tr>
<td>Increasing concentration required to inhibit growth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>North American recommendation (CLSI)†</th>
<th>European recommendation (EUCAST)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>Susceptible</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Intermediate (VISA)</td>
<td>Intermediate (VISA)</td>
<td>Resistant (VRSA)</td>
</tr>
<tr>
<td>Resistant (VRSA)</td>
<td>Use vancomycin</td>
<td>Consider alternative agent if there is evidence of clinical or microbiological failure.</td>
</tr>
<tr>
<td></td>
<td>Consider hVISA testing in patients with persistent bacteraemia and prior MRSA infection. If hVISA is identified and clinical failure is apparent, then consider an alternative agent.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Use an alternative agent other than vancomycin</td>
<td></td>
</tr>
</tbody>
</table>

†CLSI after 2006. CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; hVISA, heteroresistant vancomycin intermediate *S. aureus*; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; VISA, vancomycin intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*. © 2012 The Authors Internal Medicine Journal © 2012 Royal Australasian College of Physicians
To obtain registration, pharmaceutical companies are required to undertake randomised, controlled studies of their agent compared with vancomycin. In general, these trials have assessed non-bacteraemic patients (e.g. with complicated skin and soft tissue infections, and nosocomial pneumonia) with overall lower mortality rates compared with bacteraemic patients (e.g. those with infective endocarditis). One exception is the open-label randomised study by Fowler et al. comparing daptomycin to standard therapy for *S. aureus* bacteraemia and infective endocarditis. Based on the results of this trial, daptomycin became the first agent to be granted the indication for treatment of *S. aureus* bacteraemia (other than that caused by left-sided endocarditis) by the United States of America Food and Drug Administration.

Most registration trials are powered towards a non-inferiority end-point and thus are unable to provide insights with respect to the optimal antibiotic choice for a specific vancomycin-susceptible MRSA infection. Thus, currently, no alternative antibiotic has been shown to improve mortality, and vancomycin remains the treatment of choice for most serious MRSA infections that require intravenous therapy. The standard dosing of vancomycin in these studies is generally 1 g intravenous (IV) 12-hourly, which probably results in underdosing for the majority of patients.

Notwithstanding, concerns remain about vancomycin efficacy because of its slow bactericidal activity and variable tissue penetration, especially into lung tissue. A recent MRSA nosocomial pneumonia trial reinforces this with significantly higher microbiological and clinical responses in the linezolid arm compared with vancomycin.

**Dosing**

There has recently been increased attention to vancomycin dosing and monitoring because of concerns regarding the outcomes of severe MRSA infections treated with vancomycin and overall increases in vancomycin MIC of clinical *S. aureus* isolates.

Recommended doses from the recent Infectious Diseases Society of America MRSA treatment guidelines would in many circumstances represent increased dosing compared with the 1 g 12-hourly clinicians may be familiar with. The rationale has been to increase the likelihood of attaining the target parameter of the area under the concentration time curve (AUC) to MIC ratio (AUC/MIC), which is deemed to be the most useful pharmacodynamic parameter to predict vancomycin, with a value of $\geq 400$ desirable to eradicate *S. aureus* (Fig. 1). The consensus guidelines concluded that the target values for monitoring have increased significantly in order to achieve adequate drug exposure because of the emergence of hVISA and VISA.

Recommended vancomycin doses from recent Australian and international references are presented in Table 2. Continuous (24 h) infusion vancomycin has also been used, for example in critically ill patients and for outpatient IV therapy. While later onset of nephrotoxicity and less variability in serum concentrations of vancomycin have been claimed, the method may not lead to better patient outcomes. In this circumstance, the calculated dose recommended for a 24-h period is given as an infusion over that time, and the suggested target serum concentration is 20 mg/L.

For use in surgical prophylaxis, vancomycin is recommended in selected cases, generally as a single dose (or short course) at the loading dose or higher of the therapeutic weight-based doses. The vancomycin infusion should be completed just prior to commencement of the procedure to ensure adequate tissue concentrations at the site of surgical incision. Experience demonstrates achieving this requires significant coordination.

For treatment of *C. difficile* colitis, vancomycin is given orally. Doses in the recommended range (125–500 mg QID) achieve faecal concentrations many hundreds of times the MIC required to inhibit the growth of 90% of *C. difficile* organisms. While optimal dosing has not been explicitly defined, higher doses are recommended in severe disease, and these may allow more rapid attainment of high faecal drug concentrations.
Special populations

Renal failure

As vancomycin is cleared almost completely renally, drug accumulation can occur, and dose adjustment is required when renal function is impaired.1 Recommended starting doses are included in Table 2; subsequent doses must be based on serum concentrations.

Renal replacement therapy

Determining an appropriate vancomycin dose in patients on renal replacement therapy can be difficult given the variety of dialysis methods and frequencies used. Patient variables such as weight and residual renal function also impact on dosing.44 A detailed discussion of dosing in the various modalities of renal replacement therapy is beyond the scope of this article.

Obesity

In obese patients, the volume of distribution is smaller and clearance of vancomycin is greater, leading to a shorter terminal half-life.45 The result is that higher doses are required to achieve recommended trough serum concentrations (which can be difficult to attain). Weight-based dosing using actual bodyweight is recommended1 (Table 2); more frequent dosing (8-hourly or continuous infusion in extremely obese patients) may also be appropriate.

Paediatrics

In neonates, lower vancomycin doses are used until renal function matures (Table 2). Dosing is however controversial, and many guidelines exist.46 In infants and older children, the elimination half-life of vancomycin may be shorter than that of adults.45 A total dose of 60 mg/kg day,24 and both 6-hourly24 and 12-hourly regimens41 are currently recommended.

Vancomycin monitoring

Since the publication of the consensus guidelines, considerable debate has occurred concerning the dosing and monitoring of vancomycin.12 The Australian Therapeutic Guidelines recommend that serum concentrations should be obtained in all patients treated with vancomycin for a prolonged duration (i.e. more than 48–72 h) primarily to reduce the risk of underdosing. Although actual toxicity is uncertain, monitoring is also recommended to minimise the risk of toxicity, especially in patients with renal impairment (including those receiving renal replacement therapy and on concomitant nephrotoxins such as aminoglycosides or loop diuretics). Clinical conditions that alter pharmacokinetic parameters (volume of distribution and clearance), such as pregnancy, burns, critical illness and obesity may also warrant more aggressive monitoring.41

Pharmacokinetic and pharmacodynamic parameters

AUC/MIC

The recommended target AUC/MIC ≥400 was based on a nosocomial pneumonia study where clinical efficacy was associated with an AUC/MIC ratio greater than 345.44 In general, this target is only attainable when the MIC is ≤1 μg/mL, which is true for approximately 85% of S. aureus.19 One practical problem is the method-dependent variation in determining the MIC. The
AUC/MIC target was derived using the reference broth microdilution method; however, there can be as much as a onefold dilution difference using other widely utilised methods. The MIC method has a significant impact on the AUC/MIC ratio, and no accepted AUC/MIC targets have been derived for non-reference MIC methods. Additionally, the unexpected observation that higher vancomycin MIC was associated with poor outcomes even in flucloxacillin-treated patients suggests that other factors may potentially confound the finding of a relationship between vancomycin AUC/MIC and treatment outcome.

Trough concentrations

Traditionally, trough concentrations have been utilised for monitoring vancomycin efficacy and toxicity. The rationale behind this is that vancomycin displays time-dependent killing (like beta-lactams) rather than concentration-dependent killing (like aminoglycosides), and as serum peak concentrations have extensive inter-patient variability, trough concentrations are proposed as being more reliable. Although the best determinant of efficacy is the AUC/MIC ratio, the guidelines recommend that trough concentrations can be used as a surrogate marker as there is limited access to the more sophisticated monitoring methods utilising pharmacokinetic parameters such as AUC measurements (similar to those used for aminoglycosides). The consensus guidelines recommend that for intermittent dosing target trough serum concentrations be maintained at 15–20 mg/L for hospital-acquired pneumonia and complicated infections.

Although the best determinant of efficacy is the AUC/MIC ratio, the guidelines recommend that trough concentrations can be used as a surrogate marker as there is limited access to the more sophisticated monitoring methods utilising pharmacokinetic parameters such as AUC measurements (similar to those used for aminoglycosides). The consensus guidelines recommend that for intermittent dosing target trough serum concentrations be maintained at 15–20 mg/L for hospital-acquired pneumonia and complicated infections.

Although limited data on the clinical outcomes and costs associated with dosing based on the AUC/MIC, Kullar et al. reported that higher vancomycin trough concentrations were associated with improved patient outcomes in patients with complicated MRSA bacteraemia, and more aggressive dosing was shown to decrease overall duration of vancomycin therapy.

Alternative methods for monitoring vancomycin

Several nomograms and algorithms have been developed to individualise pharmacokinetic monitoring of vancomycin. Three major methods of dose individualisation commonly used to target specific pharmacokinetic parameters are: (i) linear regression analysis (one compartment model), (ii) population methods and (iii) Bayesian estimation procedures. Currently available algorithms and computer programs are summarised in Table 3.

Linear regression analysis

The first method used to fit serum concentrations to individual patient models was the Sawchuk-Zaske method where the patient’s pharmacokinetic parameters are calculated from at least two measured serum concentrations and assume a one-compartment model. Accurate details of dose, level, time of level and dose, duration of infusion are required in order to interpret accurately the pharmacokinetic results. Based on the pharmacokinetic results, the most appropriate dose and dosing interval adjustments for the patient are estimated.

Although these methods are relatively simple, they do make several assumptions: they only utilise serum concentration data around the dosing interval where the concentrations were obtained and cannot account other factors such as changing renal function. The lack of population data and, hence, the necessity to have two concentrations present a limitation in some settings, such as paediatrics.

Population methods

A population method, alternatively called an a priori dosing method, determines vancomycin dosage based on population pharmacokinetic parameters, without using the patient’s individual pharmacokinetic results. Several nomograms have been developed for empiric dosing of vancomycin. These nomograms make several assumptions for vancomycin: linear pharmacokinetics, strong correlation between drug clearance and calculated creatinine clearance, and dosing weight (ideal vs actual bodyweight). While the older nomograms target lower trough concentrations, there is only one nomogram that has been developed to obtain the recommended trough concentrations of 15–20 mg/L. This nomogram has only been validated in a selected group of patients, so caution should be used in the general application of the nomogram among a broad hospital population.

In general, the nomograms have proved popular, as they are easy to interpret, require no specialised pharmacokinetic knowledge for the interpretation of the results and limit use of resources (personnel and/or computers). In addition, the patient information required to interpret the nomogram is also minimal, and they only require information such as dose, concentration, time of concentration and dose.

As with all nomograms, it is important to ensure that the individual patient matches the population for which the nomogram has been developed. In addition, all nomograms assume stability of pharmacokinetic parameters, such as the rate of renal clearance of vancomycin, which may not occur in a sick patient.
<table>
<thead>
<tr>
<th>Method</th>
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<th>TCIworks</th>
<th>MM-USCPACK version 15.2</th>
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<td>Available on mobile device</td>
<td>Search data base for</td>
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<td>Generate patient report</td>
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<td>Requires a log linear calculator</td>
<td>Shows user when there is an error in data (i.e. incorrect time recorded)</td>
<td>Shows user when there is an error in data (i.e. incorrect time recorded)</td>
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<td>Patient report is lengthy and may contain too much information for patient’s chart</td>
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<td><a href="http://www.lapk.org/software.php">http://www.lapk.org/software.php</a></td>
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</table>
Bayesian estimation procedures

The Bayesian approach offers the advantage that they make optimal use of all information contained in the population model (a priori) combined with the most current pharmacokinetic information from the patient (a posteriori) to develop the patient’s most precise regimen; examples are Rxkinetics (Rxkinetics, Plattsburg, MO, USA), Target Intervention Software program (TCIworks, University of Queensland, Brisbane, Qld, Australia) and MM-USCPACK (Laboratory of Applied Pharmacokinetics, University of Southern California, Los Angeles, CA, USA). In addition, these programs can calculate doses based on a single-serum concentration and predict an appropriate starting dose providing some patient information has been entered into the program. This improves the timeliness of attaining therapeutic targets prior to steady state that potentially results in better patient outcomes especially in critically ill patients. Although these methods calculate the most precise regimen, they require healthcare practitioners (clinical pharmacologist/pharmacist) who have specialised pharmacokinetic knowledge. In addition, they require the input of patient information, such as the patient’s gender, height, weight, age, serum creatinine, dose, concentration, time of concentration and dose and duration of infusion, in order to interpret accurately the pharmacokinetic results. When utilising these monitoring software programs, users need to ensure that these programs target the current recommended AUC/MIC target ratios.

Conclusion

Vancomycin is currently the primary therapy for infections with MRSA. Vancomycin still remains an effective and cost-efficient drug with minimal toxicity and drug interactions, and years of clinical experience of use behind it. While it is clear that vancomycin should be avoided in VISA and VRSA, infections caused by these strains are infrequent.

There has been much recent debate about the monitoring of vancomycin. The current consensus guidelines concluded that the AUC/MIC ratio is the most useful pharmacodynamic parameter to predict vancomycin effectiveness and proposed a target ratio ≥400 for the optimal treatment of S. aureus infections. However, access to the more sophisticated monitoring methods utilising pharmacokinetic parameters, such as AUC, measurements, may be limited, and use of trough concentrations as a surrogate marker is an option. The recommended target trough serum concentration is 15–20 mg/L for hospital-acquired pneumonia and complicated infections.

Computerised programs, utilising the Bayesian estimation procedures, are able to achieve target concentrations in a greater percentage of patients earlier in the course of therapy than the empiric trough concentrations and population methods. When utilising these monitoring software programs, users need to ensure that these programs target the current recommended AUC/MIC target ratios. Although there are limited data on the clinical outcomes and costs associated with dosing based on the AUC/MIC, we recommend the use of these programs providing there is appropriate expertise available to make appropriate recommendations.

Acknowledgements

The authors express their sincere gratitude to the developers of the reviewed programs, for providing us with access to the required software and offering feedback on our analysis of the individual programs.

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8 Zimmermann AE, Katona BG, Plaisance KL. Association of vancomycin serum concentrations with outcomes in patients with gram-positive
Id=1214


Family refusals of registered consents: the disruption of organ donation by double-standard surrogate decision-making

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Key words
organ donation, third-party consent, informed consent, autonomy, registry, decision-making.

Abstract
Some countries such as Australia, Spain, Norway, Italy and Canada allow next of kin to override the consent of registered organ donor candidates if they personally do not concur with the donation desire of their relative. This form of surrogate decision-making represents a double standard in terms of the principle of substituted judgment (the surrogate’s duty). Further, double-standard surrogate decision-making in the setting of organ donation is a slippery slope to unethical surrogate decision-making while patients are alive. Concerns about family distress and donor candidate revocation of consent can still be managed without permitting double-standard surrogate decision-making.

Australia recorded several important milestones in the history of transplantation, including being the setting for the world’s first successful living liver donor transplant, and the world’s first single segment liver transplant in a neonate. Australia’s history of organ donation is also remarkable for having one of the lowest rates of deceased donation in the developed world (15.1 donors per million population). Australia has attempted to make strides in this area with the establishment and promotion of a national online organ donation registry. What complicates this registry is the fact that next of kin are permitted to override the consent of registered donor candidates if they personally do not concur with the donation desire of their relative. Family veto is also allowed in other countries such as Canada (uses an opt-in system whereby individuals register to be donors), as well as Spain, Norway and Italy (use a presumed consent system along with a registration system whereby individuals can formally document their desire to donate). According to the National Institutes of Health, each donor potentially helps up to 50 patients by way of solid organ and tissue transplants, so each family override can have significant clinical impact.

Family override of registered consents is an infrequent event in Australia. Between 2002 and 2011, the families of 30 donor registrants overrode their relative’s consent and prevented the following donations: 40 corneas, 16 bone donations, 4 heart valves, 4 lungs, 2 kidneys, 2 pancreata and 1 heart. (In some cases, not all of a decedent’s organs/tissues are suitable for transplant; also, families can selectively refuse and permit donation based on the organ/tissue posed.) While these veto numbers are small, to patients awaiting transplant, they are significant, and every denied donation has value. Each denied tissue donation means that patient suffering continues. Denied organ donations prevent patients from exiting the waiting list through life-saving transplants (e.g. many patients cannot tolerate bridging dialysis; there is no bridge for patients needing liver transplant; permanent ventricular assist devices or total artificial hearts are not options for all patients awaiting a heart transplant).

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Conflict of interest: None.
Additionally, one could speculate if there might be a reluctance to register to donate in the futile setting of having next of kin who knowingly will refuse to honour their donation wishes (even with advance discussions of their values). Statistically, these could represent a subset of the refusals experienced when families are approached regarding consent for unregistered relatives. The subset equates to an unmeasureable amount of donations that never could materialise because of the overt threat of family veto.

Why does Australia permit family override?

The Organ and Tissue Donation Agencies and hospital-based staff that comprise Australia’s DonateLife network indicate that the policy permitting family override is based on two assumptions: (i) not wanting to cause next of kin ‘unnecessary distress at a distressing time’; and (ii) next of kin may be aware of information indicating their relative revoked their consent but failed to change their decision on the organ donor registry.6

Ethical problems with family override

From an ethics perspective, family override can have a profound effect on the concept and practice of the form of surrogate decision-making6 known as substituted judgment. Fundamentally, surrogates are ethically obligated to make decisions that represent the values and preferences of those for whom they are agents.9 This ‘substituted judgment’ actually can free surrogates of ‘distress’ because they are honouring the expressed wishes of their loved ones – decisions that their loved one already made. Indeed, this is one of the fundamental principles of advance directives. The patient makes his/her decisions in advance, and the surrogate verbalises and honours those pre-made decisions. Research has shown that such pre-made decisions by patients can reduce the emotional burdens of families during times of medical crisis.10 Further, there are ways of dealing with dissenting families that do not involve side stepping the donor registrant’s autonomy.11,12

Organ donation registries are indeed a form of advance directive because they allow living persons to make decisions about their future. To remove organ donation from this advance decision-making creates an artificial limiter on what control patients can and cannot have with regard to their bodies. Similarly, allowing a form of surrogate decision-making, which permits families to disregard the prior expressed values and preferences of those for whom they are agents, sends the message that it is ethically permissible to have a model of surrogate decision-making that violates patient autonomy. This is concerning because such a model of decision-making could be the first step on a slippery slope allowing surrogates to override patient values and preferences (and pre-made choices in advance directives) while patients are still alive.

Specifically, the same surrogate decision-making model that allows next of kin to override registered donations could theoretically also allow next of kin to override other pre-made decisions on matters such as cardiopulmonary resuscitation, artificial feeding and hydration, artificial ventilation, and dialysis. Patients who have decided and communicated in their advance directive not to have these interventions could be forced to endure them (or vice versa) if double-standard surrogate decision-making trickles down to live patient care. These types of surrogate–patient conflicts are common in both general hospital wards as well as intensive care units.13 Families unable or unwilling to face the grief of their relative’s illness should not be allowed to take a decision-making path that relieves their distress by shifting it to another (vulnerable) party. In other words, treatment plans that cause distress for families might give relief of suffering to patients; but if families aim to avoid the distress by selecting a comfortable plan for themselves, this could in fact deliver a plan of suffering to the patient (e.g. the patient’s continued use of artificial life support because the family refuses to allow it to stop).

As an example, consider the case where a patient is alive yet neurologically devastated with only minimal brain function (and not progressing to brain death), and possesses an advance directive expressing the desire for no life-sustaining interventions (e.g. ventilator), as well as the desire to be an organ donor. The patient’s spouse might oppose both withdrawal of life support and organ donation (the scenario presented attempts to resemble a situation poised for controlled donation after cardiac death). Double-standard surrogate decision-making would complicate the patient’s life, death and organ donation.

Concurring with ethicist Bobbie Farsides, ‘The availability of clear impartial information for those who want it is a sufficient basis upon which to base the claim that those who wish to donate should be able to do so. This is so even if their statements of intent [organ donor registrations] fall short of our usual understanding of consent. . . .’14 As stated earlier, the view of Medicare Australia is...
that organ donor registration is ‘consent’. Australia’s National Health and Medical Research Council also views organ donor registration as ‘consent’, but they indicate that it is ‘a permission not a directive’.15 This could be interpreted in two ways: (i) ‘permission’ is a lower order form of consent that requires an extra step (family concurrence) in order for the donation to occur; or (ii) ‘permission’ means ‘consent for donation’, but it does not order/mandate that the donation procedure happen. Council states that the consent of the registrant has ‘ethical’, ‘emotional’ and ‘legal significance’,15 but an extra layer of consent in the form of a family veto means that the power of the family consent supersedes or negates that of the registrant.

The registration verbiage of the Australian Organ Donor Register, ‘I wish to register my intent to donate any suitable organs and tissue for transplantation’,4 announces ‘a determination to act in a certain way’16 (if clinically feasible). In reality, the determination announces a set of values about organ donation, but it cannot go farther than that because in contrast to Finns and Americans (for example), Australian donor registrants lack protections for their ‘determination’.9 Without such protections, the next of kin are truly the ‘determined’ because they are the party that ultimately permits/denies clinically feasible donation.

Questioning the validity of an organ donor registration is ethically appropriate, and registrant revocations with evidence should be honoured;4 but the questioning alone should not allow for a model of surrogate decision-making that is inconsistent with the fundamentals of substituted judgment and advance directive decision-making as this violates the registrant’s autonomy (even in death).4 Human values and dignity do not end at death, and this is evidenced by the fact that many donor registrants want their lives to have meaning after their death through organ and/or tissue donation.17 It is important to also note, however, that these same principles of substituted judgment and advance directive decision-making must also include honouring the wishes of those who have indicated they do not wish to be donors.

Agreeing with other ethicists, ‘the family veto must become a focus of policy attention’.18 Fears that honouring a registrant’s consent in the face of family refusal will contribute to a negative view of donation must be analysed in conjunction with the harms of double-standard surrogate decision-making, the denial of offered organ and tissue donations, and the harm of creating futile scenarios for some would-be registrants.19 Indeed, families are important to the donation process, and their cooperation in the process imparts important clinical and social data about the donors, but there is a difference between family cooperation and family consent. When an individual’s wishes are documented, family consent is not needed, rather families should be informed of the decision their relative already made, and educative and support services should be provided.12 Models for change have been proposed in Australia in 200420 and 2011,21 but so far, a double-standard for surrogate decision-making remains a risk for donor registrants.

Acknowledgement

The data reported here have been supplied by the Australia and New Zealand Organ Donation Registry. The interpretation and reporting of these data are the responsibility of the author and in no way should be seen as an official policy or interpretation of the Australia and New Zealand Organ Donation Registry.

Disclosure

The author is ethics consultant for the California Transplant Donor Network (a non-profit organ procurement organisation).

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Vetoing family refusals

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Thromboprophylaxis following hip and knee arthroplasty
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Abstract

Aim: To determine local thromboprophylaxis prescribing practices following arthroplasty.

Methods: A retrospective review was performed of 300 consecutive hip and knee arthroplasty patients (150 each) over a 2-year period at Tasmania’s major public hospital. The provision of thromboprophylaxis, the presence of bleeding/thrombotic risk factors and the prevalence of symptomatic venous thromboembolism (VTE) and major bleeding occurring within 90 days postoperatively were documented.

Results: The mean age of the 300 patients (169 females, 131 males) was 68.7 years (standard deviation 10.4). Only 11.3% of knee arthroplasty and 16.7% of hip arthroplasty inpatients had mechanical thromboprophylaxis documented during their stay. All inpatients received pharmacological thromboprophylaxis, predominantly injectable anticoagulants (98.4%). Only 36.5% continued to receive pharmacological thromboprophylaxis following discharge, predominantly an antiplatelet agent (55.5%). The 90-day incidence of symptomatic VTE was 2.7% (95% confidence interval: 1.0–5.0%); 4.0% (95% confidence interval: 1.0–8.0%) for knees and 1.3% (95% confidence interval: 0–5.0%) for hips. The in-hospital and post-discharge VTE incidence was 0.7% and 2.0% respectively. All readmissions for VTE occurred within 1 month of surgery.

Conclusions: While inpatient thromboprophylaxis was routine, it generally was not continued on discharge, potentially leaving many patients exposed to a higher risk of VTE. Most cases of symptomatic VTE occurred after discharge, with the majority requiring readmission to hospital under medical units. Within the limitations of a retrospective study, these findings suggest a need for further research and discussion regarding what constitutes appropriate thromboprophylaxis (type, agent and duration) following hip or knee arthroplasty.

Introduction

Venous thromboembolism (VTE), comprising pulmonary embolism (PE) and deep-vein thrombosis (DVT), accounts for over 10% of all hospital deaths and costs Australia billions of dollars each year. Depending on many intraoperative and postoperative factors, up to 60% of arthroplasty patients develop asymptomatic DVT and up to 10% will experience symptomatic VTE following their joint replacement.

The National Health and Medical Research Council (NHMRC) reports that an estimated 2000 Australians die from VTE each year. Extended-duration thromboprophylaxis has been shown to reduce significantly the frequency of symptomatic and asymptomatic VTE in arthroplasty patients. The US Agency for Healthcare Research and Quality refers to thromboprophylaxis for VTE as the ‘number one patient safety practice’. In response, many national and international bodies have created thromboprophylaxis guidelines.

Results from the Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) survey conducted in 358 hospitals in 32 countries during 2006/2007, as well as Australian evidence from almost 10 years ago, indicate that anywhere between 0.6% to 94% of at-risk surgical patients receive thromboprophylaxis following surgery. This high degree of variability in prescribing was also reported in the Evidence–Practice Gaps Report in 2003. The American Public Health Association has stated that the ‘disconnect between evidence and
execution as it relates to DVT prevention amounts to a public health crisis'.

To clarify the current situation in Australia further, we conducted a retrospective review assessing the proportion of patients who received recommended thromboprophylaxis following hip and knee arthroplasty. A secondary aim was to assess the clinical incidence of symptomatic VTE within 90 days following surgery.

**Methods**

The medical records of 300 consecutive patients who underwent a hip or knee arthroplasty (150 of each) between June 2007 and June 2009 at the Royal Hobart Hospital, Tasmania’s major public hospital, were retrieved and systematically reviewed. Where patients had multiple admissions within the review period for total hip or knee replacement surgery, only the most recent admission was included.

Data extraction included information on age, gender, operation, VTE risk factors, mode of anaesthesia, kidney function, mechanical and pharmacological prophylaxis (including duration and dosage), hospital length of stay and reported postoperative bleeding complications. Clinically symptomatic DVT and/or PE, including those causing readmission or presentation to the emergency department within 90 days of surgery, were also recorded for all patients.

The provision of thromboprophylaxis was documented during the review process, taking into account that some agents (particularly antiplatelets) were being used prior to surgery for pre-existing conditions. The thromboprophylaxis agents available during the study period at the study institution were (in alphabetical order) aspirin, clopidogrel, dipyridamole, enoxaparin, fondaparinux, unfractionated heparin and warfarin. Mechanical thromboprophylaxis was noted when patients had it recorded in their notes or on their drug chart. Prescribed thromboprophylaxis was compared with recommendations made in the American College of Chest Physicians (ACCP) consensus statement (7th ed.) on the Prevention of Venous Thromboembolism. A national guideline produced by the Australian and New Zealand Working Party was also available to surgeons during the study period; its recommendations are based on the guidelines of the ACCP and the International Union of Angiology (Table 1). A national guideline produced by the Australian and New Zealand Working Party was also available to surgeons during the study period; its recommendations are based on the guidelines of the ACCP and the International Union of Angiology (Table 1).

Pharmacological thromboprophylaxis was deemed appropriate for patients unless any of the following relative and absolute contraindications were recorded in their medical notes: bleeding disorder (e.g. haemophilia), recent central nervous system bleeding, intracranial or spinal lesion, abnormal blood coagulation, thrombocytopenia or severe platelet dysfunction, severe hepatic disease (including oesophageal varices), severe renal dysfunction (estimated creatinine clearance <10 mL/min) or pregnancy. When active bleeding events reviewed by medical staff in the hospital were judged to be critical enough to warrant cessation of thromboprophylaxis, the patient was recorded as inappropriate for receiving further thromboprophylaxis. Contraindications to mechanical thromboprophylaxis included severe cellulitis, leg deformity and severe dermatitis. To assess the suitability of the pharmacological agents and doses prescribed for each patient, renal function was estimated using the Cockcroft-Gault equation. Ideal bodyweight was estimated by entering each patient’s height and gender.
into an electronic ‘ideal body weight calculator’ produced by Therapeutic Guidelines Ltd.\textsuperscript{17}

The primary outcomes of interest were thromboprophylaxis prescribing practices and the degree to which this was consistent with contemporary recommendations. A secondary outcome measure was the incidence of symptomatic VTE (DVT, PE or VTE-related death) within 90 days following surgery. Symptomatic VTE was defined as the presence of symptoms confirmed by a positive duplex ultrasonography for DVT and positive pulmonary computed tomography angiography for PE.

The differences between groups were tested using the \(t\)-test for independence for quantitative data and the Chi-squared test for categorical variables. Pearson’s rank correlation coefficients were calculated for measuring correlations. \(P\)-values \(<0.05\) were considered statistically significant.

Ethical approval was obtained from the Tasmanian Health and Medical Human Research Ethics Committee.

### Results

In total, 300 patients (169 females, 131 males) with a mean age of 68.7 years (standard deviation (SD) 10.4) were included in the study. The mean length of stay in hospital was 6.9 days (SD 3.6) following surgery. General anaesthesia was employed in most patients, either alone (185, 63.3\%, \(n = 292\)) or in combination with neuraxial anaesthesia (48, 16.4\%, \(n = 292\)).

No patient had an absolute or relative contraindication documented in their past medical history that precluded them from receiving mechanical or pharmacological thromboprophylaxis. As such, for the purpose of this study, all patients were deemed appropriate for receiving pharmacological and mechanical thromboprophylaxis following surgery. During their hospital admission, two patients developed a bleed that warranted cessation of their pharmacological thromboprophylaxis. Both of these patients were male hip arthroplasty patients with either liver or renal impairment.

Only 42 patients (14\%) had documented use of thromboembolic deterrent stockings (TEDs). The mean BMI of patients prescribed TEDs was significantly lower than those not prescribed it (\(-2.3\) kg/m\(^2\), \(P < 0.05\), \(n = 273\)). There was no significant difference in the prescribing of mechanical thromboprophylaxis between hip and knee arthroplasty patients (\(P = 0.2\), \(n = 300\)) or between male and female patients (\(P = 0.8\), \(n = 300\)). There was also no significant difference in the median age (\(P = 0.5\), \(n = 300\)), estimated creatinine clearance (\(P = 0.2\), \(n = 289\)) or length of stay (\(P = 0.6\), \(n = 300\)) of patients who were prescribed mechanical thromboprophylaxis compared with patients who were not. No patients received documented mechanical thromboprophylaxis at discharge.

During their inpatient admission, most patients (99\%) received pharmacological thromboprophylaxis postoperatively which, in the absence of complications, was continued throughout their inpatient admission. Anticoagulants were the most commonly prescribed group of medications, and enoxaparin was the most commonly prescribed agent. Approximately one-quarter (27.7\%) of these patients were prescribed an antiplatelet and an antiplatelet agent concurrently during their inpatient stay. Excluding patients who developed a VTE or experienced a bleeding event during their admission, only 108 patients (36.5\%, \(n = 296\)) continued to receive any pharmacological thromboprophylaxis following discharge. The majority of these patients received an antiplatelet agent (60, 55.5\%, \(n = 108\)), and the rest received an anticoagulant agent (48, 44.5\%, \(n = 108\)). The remaining 188 patients (63.5\%) did not receive any agent for thromboprophylaxis on discharge (Table 2).

The majority of patients (39, 81.2\%, \(n = 48\)) discharged on an anticoagulant were newly initiated on their anticoagulant agent in hospital; the remainder were continuing agents they were using prior to their admission. The most commonly newly initiated agent was enoxaparin (34, 87.2\%, \(n = 39\)) followed by fondaparinux (4, 10.2\%, \(n = 39\)). Patients were significantly more likely to be discharged with an anticoagulant agent from the ward if they were transferring to a rehabilitation unit compared with going home (63.3\% vs 5.2\%, respectively; \(P < 0.001\), \(n = 290\)).

The majority of patients (51, 85\%, \(n = 60\)) discharged on an antiplatelet were taking their antiplatelet agent prior to surgery, and only 15\% were newly initiated on one in hospital. Aspirin was the most commonly prescribed antiplatelet agent.

When the agent, dose and duration of therapy prescribed for each patient discharged home (not previously on an anticoagulant) was compared with the ACCP recommendations, only 9\% of knee arthroplasty (10, \(n = 113\)) and 1\% (1, \(n = 103\)) of hip arthroplasty patients

### Table 2: Thromboprophylaxis prescribing for inpatients and on discharge from the orthopaedic ward

<table>
<thead>
<tr>
<th>Agent</th>
<th>Inpatient (n = 298) (%)</th>
<th>Discharge (n = 294) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>247 (82.9)</td>
<td>30 (10.2)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1 (0.3)</td>
<td>60 (20.4)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>37 (12.4)</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>8 (2.7)</td>
<td>13 (4.4)</td>
</tr>
<tr>
<td>Heparin</td>
<td>2 (0.7)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>No agent</td>
<td>3 (1.0)</td>
<td>186 (63.3)</td>
</tr>
</tbody>
</table>

\(P\)-values \(<0.001\).
received the recommended therapy (agent, dose and duration). The remaining patients either received no thromboprophylaxis or received it at an inappropriate dose and/or duration (Fig. 1).

The overall incidence of symptomatic VTE within 90 days of surgery was 2.7% (95% confidence interval: 1.0–5.0%). The incidence in knee arthroplasty patients was 4.0% (95% confidence interval: 1.0–8.0%; four DVT, one PE and one DVT + PE). The incidence in hip arthroplasty patients was 1.3% (95% confidence interval: 0–5.0%; two DVT). Five of these patients experienced DVT, one patient experienced PE and one patient experienced both DVT and PE. The in-hospital VTE incidence was 0.7% (2, n = 300) and occurred at 4 and 5 days, respectively, following surgery. One patient experienced both DVT and PE, the other experienced only a DVT. Both patients were using anticoagulant thromboprophylaxis at the time the clot occurred.

VTE occurred in 2% of patients (five DVT, one PE, n = 296) following discharge (excluding patients who experienced a bleed or VTE in hospital). Four of these patients were readmitted to the hospital for a median of 2.5 days to receive VTE treatment under a medical team (range: 1 to 6 days). The median time to VTE occurrence outside of hospital was 11.0 days (range: 7 to 31 days). Of the patients who suffered a thromboembolic event following discharge, only one patient had been prescribed an anticoagulant medication at discharge. This patient had been using warfarin prior to surgery and was discharged with warfarin and enoxaparin to cover until the International Normalised Ratio (INR) was therapeutic. It is uncertain if the INR was therapeutic at the time of the event, 6 days following discharge. The remaining five patients who developed VTE following discharge did not receive the ACCP-recommended course of thromboprophylaxis for their surgery type. No significant risk factors were identified for developing VTE following surgery.

**Discussion**

In-hospital thromboprophylaxis was routine with most patients receiving an anticoagulant agent. Interestingly, despite the bleeding risk concerns associated with anticoagulant agents, over 25% of patients received both an antiplatelet and anticoagulant agent during their inpatient stay.18 Notably, this study determined that over 60% of patients did not receive any documented thromboprophylaxis, either pharmacological (antiplatelet/anticoagulant) or mechanical, on discharge from hospital. When comparing prescribing practices with the ACCP guidelines available during the study period, overall less than 6% of patients discharged home received complete courses of thromboprophylaxis. This was predominantly due to a shortfall in the duration of therapy prescribed.

There was a trend towards patients undergoing knee arthroplasty being more likely to receive the full course of treatment compared with patients undergoing hip arthroplasty (9% vs 1%). This is likely to be due to the average length of stay in hospital (6.9 days, SD 3.6) being considerably closer to the recommended duration of thromboprophylaxis for knee arthroplasty (at least 10 days) compared with hip arthroplasty patients (28 to 35 days). In the absence of bleeding complications, all patients received inpatient thromboprophylaxis.
throughout their admission. This meant that hip arthroplasty patients were more reliant on thromboprophylaxis being prescribed for them after discharge from the ward. This only occurred in 17 cases (12.9%, n = 132) and typically for a much shorter duration than was required (13, 76.5%) to complete the recommended 28 to 35 days of treatment.

This study demonstrated an in-hospital and 90-day VTE incidence of 0.7% and 2.0% respectively. These rates are comparable with other studies in the literature.2,19 The majority of VTE occurred following discharge, which has also been previously reported in the literature.5,19–21 As all readmissions to hospital for VTE treatment were under medical units, local VTE incidence following arthroplasty may be underestimated by surgical teams. In their study, Gallagher et al. reduced the VTE incidence at an Australian hospital by over 70% through the use of various interventions aimed at increasing thromboprophylaxis prescribing in line with the ACCP recommendations.22 Whether surgeons should default to adopting any particular guideline is still highly debated; however, the low number of patients receiving any thromboprophylaxis (multimodal, mechanical or pharmacological) post-discharge in this study suggests a need for further research to investigate factors that impact on prescribing habits.

There were several limitations to this study. It was retrospective in nature and relied solely on documentation in hospital records to identify thromboprophylaxis use, possible contraindications, and thrombotic and bleeding events. The retrospective nature of the study introduced potential bias favouring low rates of thromboprophylaxis prescribing following hospital discharge, as although there were no thromboprophylaxis specific recommendations on discharge summaries sent to general practitioners, it is possible that general practitioners may have independently prescribed it for their patients after discharge. In addition, these limitations introduce potential bias for low-reported VTE incidence as all cases of out-of-hospital diagnosed and treated VTE may not have presented to the study hospital. The fact that the study institution is the only public hospital within the area should have minimised this potential limitation, although it is feasible that some patients may have been admitted to one of several private hospitals in the area or treated directly by their general practitioner.

The NHMRC guideline on the prevention of venous thromboembolism in Australian hospitals (released November 2009) was not available during the data collection period, nor was the National Institute of Clinical Excellence VTE prevention guideline (released 2010).2 Additionally, as there was no risk stratification tool coupled with the American Academy of Orthopaedic Surgeons (AAOS) 2007 guideline, and aspirin and warfarin doses prescribed by surgeons at the participating hospital were markedly different to those recommended by the guideline (indicating they were being prescribed primarily for cardiac and stroke prevention), the AAOS recommendations were considered unsuitable for comparison with the data presented here.23

The retrospective nature of the study did not allow the researchers to analyse potential barriers to thromboprophylaxis. One potential barrier to thromboprophylaxis prescribing identified by the NHMRC is the perceived and actual risk of major bleeding associated with pharmacological prophylaxis.5 In particular, surgeons may be understandably reluctant to expose patients to the risk of excessive intra- or post-operative bleeding and the subsequent complications, especially in procedures such as joint replacement where bleeding can lead to severe infections and a need to explant prostheses.2 Being a retrospective study, it was not possible to determine if such perceived risks affected thromboprophylaxis prescribing, particularly at discharge. A further limitation to this study is the lack of data collected on infection rates following these surgeries.

The release of the 2009 NHMRC guideline has fuelled discussions on thromboprophylaxis following hip and knee arthroplasty patients. In response to the NHMRC guideline, the Arthroplasty Society of Australia (ASA) released an article with recommendations for surgeons to conduct risk assessments for each patient and to refer to their recently published guideline.18,24 Within this guideline, the ASA recommend aspirin (or no chemotherboprophylaxis) with mechanical thromboprophylaxis as an option for patients with a relatively low risk of VTE (a ‘multimodal approach’) (NB: the guideline does not provide a risk stratification tool to assist surgeons identify patients with a low risk of VTE). Furthermore, the recently released ACCP Guidelines on the Prevention of VTE in Orthopedic Surgery Patients (9th Edition) recommend aspirin as an option for sole thromboprophylaxis (Grade 1B).25

**Conclusion**

Despite the limitations to this study, its findings indicate that the lack of consensus on what constituted appropriate thromboprophylaxis following hip and knee arthroplasty during the study period left most patients without ACCP-recommended, NHMRC-recommended or ASA-recommended thromboprophylaxis. The findings suggest that the implementation of guidelines requires that more be done than simply publishing them.26
References


Survival of myeloma patients following the introduction of thalidomide as a second-line therapy: a retrospective study at a single New Zealand centre

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Key words
multiple myeloma, survival, thalidomide, stem cell transplantation.

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Abstract

Aim: This retrospective study compares the overall survival (OS) of multiple myeloma (MM) patients following treatment at a New Zealand hospital over a period in which novel therapies were available but restricted, almost exclusively, to thalidomide as a second-line therapy.

Methods: Clinical, laboratory and OS data were collected on 361 MM patients who were treated at Christchurch Hospital during 2000–2010. Patients were subdivided according to the clinical criteria used to determine front-line treatment decisions. Older patients (age ≥66, n = 180) generally received standard-dose chemotherapy without autologous stem cell transplant (SCT) and formed one group. Younger patients were further subdivided according to whether they received autologous SCT (n = 89), allogeneic SCT (n = 24) or no SCT (n = 68).

Results: Older patients had a significantly shorter OS (P < 0.0001) than younger patients (median OS = 25 vs 78 months) however treated. Analysis of relative survival demonstrated that the increased mortality of older patients was greater than that attributable to normal ageing. Younger patients who received no transplant had a significantly shorter OS (P < 0.0001) than those who received autologous SCT or allogeneic SCT with 5-year survivals of 38%, 70% and 72% respectively. Use of novel therapies was significantly higher in younger than older patients (60% vs 47%, P = 0.011).

Conclusions: The front-line treatment groupings of hospital MM patients had significantly different survivals. The OS of SCT ineligible patients remains poor despite the introduction of thalidomide.

Introduction

Multiple myeloma (MM) accounts for approximately 10% of all haematological malignacies. Despite considerable advances in its treatment, MM remains incurable with a 5-year relative survival of less than 50%.1,2 For many years, combination chemotherapy with melphalan and prednisone, used since the 1960s, remained a common front-line treatment option for older patients. In younger patients, high-dose melphalan (HDM) with autologous stem cell transplantation (SCT) used as consolidation after a multi-drug induction has become standard front-line therapy.3,4 Allogeneic SCT currently provides the only potentially curative myeloma treatment, but its high treatment-related mortality and uncertainty over its optimal usage has restricted its application.3

In the past decade, the emergence of the novel therapies thalidomide, lenalidomide and bortezomib has dramatically changed the therapeutic landscape. Although initially used for relapsed or refractory disease, these agents are now increasingly being used throughout North America and Europe as part of front-line therapies.4

PHARMAC is the organisation within New Zealand (NZ) which manages District Health Board (DHB) spending on pharmaceuticals, by determining the indications for which drugs may be taxpayer funded, according to
criteria which include patients' needs, availability of other treatments, value for money and government health priorities. During the period of this study, starting in 2000, PHARMAC funded thalidomide for second-line or subsequent treatment of myeloma, but did not fund bortezomib or lenalidomide. These decisions have contributed substantially to the treatment algorithm in NZ.

Data on myeloma patient survival have been derived predominantly from clinical trials and population studies. Clinical trial data are difficult to apply to the general patient population due to both their exclusion of patients with poor performance and co-morbidities and their use of newer treatment strategies at disease progression. In contrast, population studies provide an accurate measure of the overall survival (OS) of all MM patients. However, most such studies do not include detailed treatment information and therefore do not allow estimation of the OS of patients who fall into distinct clinical groupings. To address some of these limitations, we undertook a hospital-based survey, aiming to provide 'real-life' information of value to patients, their doctors and the health systems in which they are treated. We have studied the course of all patients with myeloma who received treatment in Christchurch, NZ, between 2000 and 2010, examined patient outcomes and compared these with results from other settings where there may have been more extensive use of novel therapies.

**Methods**

**Data collection**

All MM patients diagnosed between January 2000 and October 2009 who received treatment at Christchurch Hospital were identified using the Christchurch Hospital Haematology Department database. Information on disease, treatment and treatment outcomes was obtained from electronic and written hospital records. Information on use of thalidomide was also supplied by Medsafe (the NZ Government agency that regulates prescribing of thalidomide). Patients were staged according to the International Staging System for MM. The median age of this series of patients was used to categorise patients into younger and older groups, and each age category was independently analysed.

**Treatment**

There was little variation in standard treatment outside clinical trials during the study period. Suitable younger patients received induction with vincristine, adriamycin and dexamethasone or cyclophosphamide and dexamethasone, followed by HDM (melphalan 200 mg/m²) and a single autologous SCT. Post-transplant consolidation therapy or maintenance therapy was rarely used. Selected younger patients with fully matched sibling donors proceeded to a staged reduced intensity conditioned (RIC, fludarabine 90 mg/m² and 200 cGy total body irradiation) allogeneic SCT after recovery from HDM and autologous SCT. Occasionally, patients received allogeneic transplantation with myeloablative conditioning without prior autologous SCT. Older patients generally received melphalan and prednisone as first-line therapy. Thalidomide was funded and utilised as monotherapy or in combination for treatment of refractory or relapsed myeloma but was not used as first-line treatment. Eligible patients could participate in one or more investigator-initiated or industry-sponsored trials that were conducted during this study period. Patients who received treatment with bortezomib and/or lenalidomide did so only within the context of industry-sponsored trials.

**Evaluation of response**

Disease response was evaluated following SCT or completion of induction therapy. Response criteria were based on the International Uniform Response Criteria for MM. Briefly, complete response (CR) required no detectable serum M-protein. Very good partial response (VGPR) was defined as >90% reduction in serum M-protein and partial response as >50% reduction in serum M-protein. Progressive disease (PD) required an increase of >25% in serum M-component, with the absolute increase greater than or equal to 0.5 g/dL or the reappearance of M-protein in patients previously in CR. Serum M-protein at diagnosis was used as the reference point for evaluation of the maximal response achieved following SCT. The lowest serum M-protein value reached following SCT or induction therapy was used as the reference point for detection of PD subsequent to the maximal response.

**Statistical analysis**

Patients were followed up until October 2010. Differences in categorical variables were evaluated by chi-squared statistics. The primary clinical outcome analysed for the entire cohort was OS, calculated from the date of diagnosis until death from any cause. In addition, for younger patients who received autologous SCT (or intermediate-dose melphalan (IDM)), OS was also calculated from the date of SCT (or IDM) until death from any cause. Progression-free survival (PFS) was calculated from the date of SCT until the date of PD or death from any cause. OS and PFS distributions were plotted using...
Kaplan–Meier plots and compared by the log rank test. In order to calculate relative survival, the expected survival probability of an age- and sex-matched normal population was estimated using the Ederer II method based on national life expectancy data from Statistics New Zealand. The cumulative relative survival (the ratio of overall and expected survival) was calculated using the SURVSOFT software package (Bavarian Cancer Registry, Erlangen, Germany). Relative survivals at each time point were compared using Z-scores. Differences were considered to be statistically significant if the corresponding \( P \)-value was \( \leq 0.05 \). All statistical analysis except for calculations of relative survival was performed using SPSS software (version 19) (IBM SPSS, Chicago, IL, USA).

### Results

#### Patient characteristics

Three hundred and sixty-one previously untreated MM patients were included in the study, ranging in age from 32 to 94 years. Patient characteristics are given in Table 1. The majority (298) had received their diagnosis and all of their treatment in Christchurch. The remaining patients, predominantly younger, had been referred from other DHBs for SCT only. This had the effect of reducing the median age of the whole population from 69 years (Christchurch patients only) to 66 years (all patients). Those over and under the median age of 66 years are henceforth described as older (180 patients) and younger (181 patients) respectively. Among younger patients, there were three clearly discernible treatment groups – those who received allografts, those who received autografts without subsequent allograft and those who did not receive any SCT.

![Table 1: Patient characteristics](image)

<table>
<thead>
<tr>
<th></th>
<th>Older</th>
<th>Younger</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>180</td>
<td>181</td>
<td>361</td>
</tr>
<tr>
<td>Deceased</td>
<td>131</td>
<td>71</td>
<td>202</td>
</tr>
<tr>
<td>Survivor FU‡</td>
<td>39</td>
<td>49</td>
<td>44</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>62%</td>
<td>64%</td>
<td>63%</td>
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<tr>
<td>Age§</td>
<td>Median</td>
<td>76</td>
<td>56</td>
</tr>
<tr>
<td>M-protein¶</td>
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<td></td>
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<tr>
<td>IgG</td>
<td>58%</td>
<td>62%</td>
<td>56%</td>
</tr>
<tr>
<td>IgA</td>
<td>28%</td>
<td>20%</td>
<td>23%</td>
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<tr>
<td>Light chain</td>
<td>12%</td>
<td>18%</td>
<td>16%</td>
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<tr>
<td>ISS (%)††</td>
<td></td>
<td></td>
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<tr>
<td>1</td>
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<td>—</td>
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</tr>
<tr>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Received auto SCT</td>
<td>6 (3%)</td>
<td>110 (61%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

---

### Treatment received

Treatments received by patients are summarised in Table 1. In the older patient group, the predominant treatment received was standard-dose chemotherapy, with only a small proportion (3%) receiving autologous SCT. Among the younger patients, the predominant treatment included HDM with autologous SCT. A subset of younger patients received an allogeneic SCT (\( n = 24 \)). The majority of these patients had first received an

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autologous SCT \((n = 17)\) or intermediate doses of melphalan \((n = 4)\) and were then treated with RIC allogeneic SCT. Three younger patients received myeloablative allografts without prior autologous SCT and were included for analysis of OS from diagnosis with the other allografted patients (Table 1). A substantial proportion (38%) of younger patients did not receive SCT. Three of these patients had been randomly allocated to no transplant within a clinical trial, whereas the decision to avoid SCT in the remainder was based on patient co-morbidities, patient or physician preference.

During the study period, 183 (51%) patients received thalidomide, which was the principal novel therapy used for treatment of PD or relapse. Thalidomide was not used as maintenance therapy except in six patients post autologous SCT who participated in a clinical trial. Bortezomib and/or lenalidomide were only used in relapsed disease for 44 (12%) patients who participated in one or more clinical trials. Of those patients who received bortezomib or lenalidomide, 80% had also received treatment with thalidomide. Overall novel therapies were prescribed to 193 (53%) of all patients during the study period with significantly higher levels of prescription in younger patients than older patients (60% vs 47%, \(P = 0.011\)). When analysis was restricted to those patients who had died during the course of the study, and had therefore all potentially experienced relapse events, a more pronounced difference between younger and older patients was observed with respect to novel therapy usage (77% vs 43%, \(P < 0.0001\)).

**Outcome of treatment by age**

When analysed as a single group, MM patients had a significantly shorter OS than an age- and sex-matched NZ population with a 5-year survival of 41% (Table 2, Fig. 1a). Older patients had a significantly shorter OS \((P < 0.0001)\) than younger patients even when compared with those younger patients who had not received a transplant (Fig. 1b, Table 2). The prognostic significance of age was further examined by subdivision of patients into age quartiles. Those patients aged >75 had a significantly shorter OS \((P < 0.001)\) than those aged 66–75 (median = 15 vs 37 months). There was no significant difference in OS between patients aged <57 and those 57–66 (Fig. 1c).

Within the general population, older and younger individuals have significantly different expected survivals. These differences in background mortality will naturally contribute to the lower observed survival of older myeloma patients. In order to adjust for this effect, myeloma patient groups were also compared using relative survival, in which patient survival was expressed as a ratio compared with the expected survival in a corresponding age- and sex-matched NZ population. Older patients had a significantly shorter relative survival than younger patients at each time point \((P < 0.001)\), and at 2 years, this difference was 26% (95% confidence interval = 16–36%, \(P < 0.0001\)). These differences demonstrate that the increased mortality in the older patients was greater than that which can be attributed to the normal effects of older age (Fig. 1d).

**Outcome following SCT**

The effects of autologous and allogeneic SCT were examined only in the younger patient group because few older patients had any SCT. Younger patients who received an allogeneic or autologous SCT had a significantly longer OS than those who did not receive an SCT (Table 2,
Death within 100 days of transplant occurred in 5% of each of the autologous SCT and RIC allogeneic SCT groups. After autograft, the CR/VGPR rate was 48%. There was no significant increase in CR/VGPR for those who proceeded to RIC allograft. From the time of autologous SCT (or IDM), there was no significant difference in PFS or OS between patients who completed their frontline treatment with autologous SCT and those who proceeded to RIC allograft (Table 2, Fig. 2). From the time of progression, there was no significant difference ($P = 0.281$) in the OS of patients who had received autologous SCT and those who had also received RIC allogeneic SCT (median OS = 50 months vs not reached, data not shown).

Only three younger patients received myeloablative allografts without prior autograft. Two remain alive without evidence of disease 5 and 10 years after diagnosis.

**Discussion**

We present the results of a retrospective analysis of MM patients treated in our centre over a period following the introduction of thalidomide as an available second-line therapy. The results demonstrate the significant
associations that age and treatment type have with the OS of myeloma patients. To our knowledge, there have been no similarly published data for a NZ population. The data are strengthened by calculating relative survival rates for different ages as well as OS.

Population studies have reported that the OS of older MM patients is poor and, unlike that of younger patients, has either not improved or improved only slightly, following the introduction of novel therapies. The survival of older patients in the current study was similar to that reported in population-based studies of patients treated since the introduction of novel therapies. The OS estimates are, however, considerably shorter than those reported in prospective clinical trials of older patients where novel therapies were used as a second-line therapy (median OS = 16 vs 29–50 months). This difference probably reflects the patient selection that occurs in trials. However, differences between real-world settings and clinical trials with respect to the rate of novel therapy usage may also have made an impact. It is therefore notable that in the current study, only 47% of older patients received novel therapies, restricted mainly to thalidomide at relapse. The reason why this number is not higher is not discernible, but it is in keeping with novel therapy usage rates at relapse in other published studies in the elderly. It is possible that clinician preference over the study time period was to use less NA in the very old patients.

The results of this study underline the poor survival of older patients even when compared with those younger patients not receiving SCT. This was still evident when the normal effects of ageing were adjusted for by comparing survival to that of an age- and sex-matched population. Older patients are generally treated less aggressively, do not receive autologous SCT and have a lower rate of novel agent administration than their younger counterparts. It is therefore tempting to consider increasing the intensity of the treatment approach for these patients when patient co-morbidities and performance status permit.

In otherwise healthy patients aged <60–70, autologous SCT is now considered the gold standard front-line treatment. Surprisingly, more than one-third of younger patients in this study did not receive an SCT. It is unclear whether this is a higher proportion than expected in a general hospital setting, as little comparable published data are available. However, one population study has reported that only 36% of patients aged less than 65 received an SCT while this proportion was 78% in a trial referral population aged less than 60. Although a meta-analysis of prospective randomised clinical trials did not clearly demonstrate that autologous SCT provides any survival benefit when compared with standard-dose chemotherapy, younger patients in the current study who did not receive autologous SCT had a significantly poorer OS than those who did. Information pertaining to the reasons why some younger patients did not receive an SCT was unavailable, but it is likely that those who received no transplant had higher frequencies of co-morbidities and other adverse health factors. Thus, it is not possible to disentangle the effects of patient selection and treatment efficacy on the OS of these patients. The relatively poor prognosis of those younger patients ineligible for SCT is in agreement with other reports and underlines the requirement for new therapies in this group.

Previous studies on patients treated with autologous SCT prior to the widespread introduction of novel therapies had similar PFS but substantially lower OS than those observed in this study. The improved OS of autologous SCT patients in NZ is similar to that reported in other general hospital studies of autologous SCT patients treated since the availability of novel therapies. A subset of patients received allografts, predominantly RIC allogeneic SCT. The small number of patients analysed precludes any meaningful comparison of allogeneic and autologous SCT. The data are, however, in line with other studies that indicate that any benefits from allo-grafting can only apply to a small percentage of patients after prolonged follow up.

The optimal usage of novel therapies remains unclear and may require substantially longer follow-up times to become evident. In the current study, thalidomide was available at first relapse, but relapse data were only available for transplant patients. Consequently, the data cannot be used to analyse directly the benefits of thalidomide at relapse in non-transplant patients.

In the interpretation of our results, a number of limitations must be considered. The retrospective nature of the analysis, the relatively small number of patients and the disparate patient composition in the different treatment groups together with the limited information regarding prognostic markers and additional outcome measures make it possible to draw only broad conclusions. Similarly, the paucity of other published data on the relative outcomes of the major MM patient groupings in a general hospital setting makes comparisons of this study’s results with those in other centres problematic. Data from clinical trials and population studies can provide only a broad indicator of expected OS due to differences in patient selection and the availability of treatment detail. However, despite these caveats, this study provides useful information about the real life outcomes of a complete and unselected MM patient
population at a single tertiary NZ hospital. These patients were treated within the tightly defined and relatively restricted criteria that have applied to the use of novel therapies in NZ. In May 2011, the NZ access and funding criteria for novel agents changed such that bortezomib can now be used either first or second line, and thalidomide may now be used for any patient with myeloma at any time during treatment. The data in this present study will serve as a useful baseline for future comparison of outcomes in myeloma in an era of increased novel agent usage.

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We thank all our colleagues in the haematology units in the South Island of New Zealand for their constant care of patients with myeloma.

References


Most individuals with treated blood pressures above target receive only one or two antihypertensive drug classes

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1St Vincent’s Institute of Medical Research, 2St Vincent’s Health, 3University of Melbourne, 4Monash University, 5Baker IDI Heart and Diabetes Institute and 6Bupa Australia, Melbourne, Victoria, Australia

Abstract

Background: A significant proportion of individuals taking antihypertensive therapies fail to achieve blood pressures <140/90 mmHg. In order to develop strategies for improved treatment of blood pressure, we examined the association of blood pressure control with antihypertensive therapies and clinical and lifestyle factors in a cohort of adults at increased cardiovascular risk.

Methods: A cross-sectional study of 3994 adults from Melbourne and Shepparton, Australia enrolled in the SCReening Evaluation of the Evolution of New Heart Failure (SCREEN-HF) study. Inclusion criteria were age ≥60 years with one or more of self-reported ischaemic or other heart disease, atrial fibrillation, cerebrovascular disease, renal impairment or treatment for hypertension or diabetes for ≥2 years. Exclusion criteria were known heart failure or cardiac abnormality on echocardiography or other imaging. The main outcome measures were the proportion of participants receiving antihypertensive therapy with blood pressures ≥140/90 mmHg and the association of blood pressure control with antihypertensive therapies and clinical and lifestyle factors.

Results: Of 3623 participants (1975 men and 1648 women) receiving antihypertensive therapy, 1867 (52%) had blood pressures ≥140/90 mmHg. Of these 1867 participants, 1483 (79%) were receiving only one or two antihypertensive drug classes. Blood pressures ≥140/90 mmHg were associated with increased age, male sex, waist circumference and log amino-terminal-pro-B-type natriuretic peptide levels.

Conclusions: Most individuals with treated blood pressures above target receive only one or two antihypertensive drug classes. Prescribing additional antihypertensive drug classes and lifestyle modification may improve blood pressure control in this population of individuals at increased cardiovascular risk.

Key words
hypertension, medication, blood pressure target, population cohort, cardiovascular risk.

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Introduction

High blood pressure (BP) is increasingly common as people age. More than half of people aged 60 years and approximately three-quarters of those aged ≥70 years develop hypertension with systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg (BP ≥140/90 mmHg), and its prevalence is expected to increase with the ageing of society. Worldwide, suboptimal BP (SBP >115 mmHg) is the number one attributable risk factor for death, being responsible for 54% of cerebrovascular disease and 47% of ischaemic heart disease, and BP ≥140/90 mmHg is responsible for 20% of heart failure and 23% of chronic kidney disease. Yet, despite the ready availability of antihypertensive therapies and the well-established benefits of reducing BP, only half of people taking these medications achieve a BP < 140/90 mmHg.

Identifying characteristics associated with failure to reach target BP may aid development of strategies for improved management of hypertension and prevention of cardiovascular and renal disease. The SCReening Evaluation of the Evolution of New Heart Failure (SCREEN-HF) study is a community-based evaluation of the use of plasma amino-terminal-pro-B-type natriuretic peptide (NT-proBNP) to identify individuals with cardiac dysfunction (as assessed by echocardiography) and increased risk of heart failure and other cardiovascular events. SCREEN-HF study participants were volunteers aged ≥60 years with self-reported cardiovascular risk factors who were predominantly privately insured. A previous survey showed Australians of higher socioeconomic background and living in metropolitan areas have lower BP. Thus, SCREEN-HF study participants represented a ‘best-case’ scenario for BP control. We report the blood pressure data from the baseline visit of individuals enrolled in the SCREEN-HF study, the proportion of participants receiving antihypertensive therapy with BP ≥140/90 mmHg and the association of elevated BP with antihypertensive therapies and clinical and lifestyle factors.

Methods

Study population

A flow chart describing the recruitment strategy is shown in Figure 1. Letters of invitation and a questionnaire were sent to 44 000 Hospital Benefits Association (HBA) members aged ≥60 years who lived in Melbourne or Shepparton, Victoria. There were 11 128 returned questionnaires, and 9764 consecutive respondents were screened by phone until target recruitment was reached. Baseline study visits were conducted at Dorevitch Pathology collection centres where a study nurse consented, interviewed and examined the participant and collected a non-fasting blood sample for measurement of electrolytes, creatinine, urea, glucose, full-blood examination and NT-proBNP. Of 4058 individuals attending the baseline study visit, 3992 met the inclusion and exclusion criteria and had blood pressure and plasma NT-proBNP measurement, and 3658 (92%) were HBA members. Inclusion criteria were age ≥60 years with one or more of self-reported myocardial infarction or other ischaemic or valvular heart disease, atrial fibrillation, cerebrovascular disease, renal impairment or treatment for hypertension or diabetes for ≥2 years. Exclusion criteria were known heart failure or cardiac abnormality on previous echocardiography or other cardiac imaging. Recruitment commenced in May 2007 and was completed in January 2010.

Study variables

Blood pressure

BP measurement was performed with the participant in a seated position after at least 5 min rest. An appropriate
cuff size was used, the arm was supported by a table at heart level, and the BP was measured with an automatic BP monitor (A&D Medical, Melbourne, Victoria, Australia). Two readings were taken 3 min apart and recorded. In the present analysis we used the mean of these two readings.

**Clinical factors**

Height, weight and waist circumference were measured at interview, and age, sex, past medical history including ischaemic heart disease (myocardial infarction, angina, coronary revascularisation), valvular or other heart disease or heart surgery, hypertension, respiratory disease, renal impairment, cardiac arrhythmia including atrial fibrillation, cerebrovascular disease, diabetes, peripheral vascular disease (including aortic and carotid disease), obstructive sleep apnoea and pacemaker use were recorded. Self reported details of lifestyle factors included smoking history and alcohol intake. Participants brought details of their medications to the baseline study visit, which were recorded. All blood tests were performed by Dorevitch Pathology (Heidelberg, Victoria) and estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study equation. Plasma NT-proBNP was measured by electrochemiluminescence immunoassay using an Elecsys instrument (Roche Diagnostics, Basel, Switzerland) and the lower limit of detection was 0.6 pmol/L.

**Ethics approval**

The SCREEN-HF study was approved by the Alfred Human Research Ethics Committee and written informed consent was obtained from all the participants.

**Statistical analysis**

All analyses were conducted using Statview 5.0.1 (SAS Institute, Cary, NC, USA). Summary statistics were percentages for categorical variables and medians with 25th and 75th percentiles for continuous variables. Differences between groups were tested with $\chi^2$ or Fisher’s exact tests for categorical variables and Mann-Whitney U-tests for continuous variables. Multivariable logistic regression analysis was used to identify associations between BP ≥ 140/90 mmHg and clinical and lifestyle factors for which $P < 0.1$ in univariate analysis; given its skewed distribution, log NT-proBNP was entered into the model. Statistical significance was interpreted as a two-tailed $P < 0.05$.

**Figure 1** Flow chart of numbers of individuals invited to participate in the SCReening Evaluation of the Evolution of New Heart Failure study who were subsequently enrolled.

![Flow chart](image-url)
Table 1 Baseline characteristics of 3623 SCReening Evaluation of the Evolution of New Heart Failure study participants receiving antihypertensive therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SBP &lt; 140 and DBP &lt; 90 mmHg (n = 1756)</th>
<th>SBP ≥ 140 and/or DBP ≥ 90 mmHg (n = 1867)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 (65–75)</td>
<td>70 (65–76)</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>442 (25%)</td>
<td>536 (29%)</td>
</tr>
<tr>
<td>Male</td>
<td>883 (50%)</td>
<td>1092 (58%)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129 (121–134)</td>
<td>152 (145–161)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76 (70–81)</td>
<td>86 (79–92)</td>
</tr>
<tr>
<td>NT-proBNP (pmol/l)</td>
<td>12 (6–24)</td>
<td>13 (7–27)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>203 (123)</td>
<td>150 (83)</td>
</tr>
<tr>
<td>Other ischaemic heart disease</td>
<td>383 (223)</td>
<td>327 (183)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>74 (43)</td>
<td>72 (43)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>178 (100)</td>
<td>153 (83)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>175 (100)</td>
<td>162 (103)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>37 (23)</td>
<td>40 (23)</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>28 (23)</td>
<td>28 (23)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>294 (17%)</td>
<td>327 (173)</td>
</tr>
<tr>
<td>eGFR &gt;60 mL/min/1.73 m²</td>
<td>457 (261)</td>
<td>405 (223)</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>128 (73)</td>
<td>139 (73)</td>
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<tr>
<td>Tobacco use:</td>
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<td></td>
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<tr>
<td>Current smoker</td>
<td>50 (33)</td>
<td>72 (43)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>809 (463)</td>
<td>854 (463)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>897 (513)</td>
<td>941 (503)</td>
</tr>
<tr>
<td>Alcohol &gt;2 drinks/day</td>
<td>301 (173)</td>
<td>411 (223)</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>943 (543)</td>
<td>934 (503)</td>
</tr>
<tr>
<td>Aspirin therapy</td>
<td>762 (430)</td>
<td>740 (403)</td>
</tr>
<tr>
<td>NSAID therapy</td>
<td>135 (83)</td>
<td>175 (91)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>99 (91–107)</td>
<td>100 (92–108)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28 (25–31)</td>
<td>28 (25–31)</td>
</tr>
</tbody>
</table>

Data shown as median (interquartile range) or n (%). Other ischaemic heart disease refers to angina and/or coronary revascularisation. Data for cardiovascular disease, diabetes, obstructive sleep apnoea, smoking, alcohol intake and drug therapy were from self-report. DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug; NT-proBNP, amino-terminal-pro-B-type natriuretic peptide; SBP, systolic blood pressure.

Results

Participants

Of 3992 participants with blood pressure and NT-proBNP data, 3623 were receiving antihypertensive therapy, and 369 were not. Of the 3623 receiving antihypertensive therapy, 1867 (52%) had BP ≥ 140/90 mmHg (Table 1), whereas, of the 369 not receiving antihypertensive therapy, 161 (44%) had BP ≥ 140/90 mmHg. We did not formally estimate cardiovascular risk because plasma lipids were not measured. However, 2347 (65%) of participants receiving antihypertensive therapy were aged ≥75 years and/or had existing cardiovascular disease, diabetes or eGFR < 60 mL/min/1.73 m² that placed them at >15% absolute risk for a cardiovascular event in the next 5 years; yet, despite their high-cardiovascular risk, 1180 (50%) had BP ≥ 140/90 mmHg. Among the 3008 participants receiving antihypertensive therapy who were not known to be diabetic, 12 had a random plasma glucose level >11 mmol/L, indicative of undiagnosed diabetes. Of the 2094 participants receiving antihypertensive therapy who had self-reported cardiovascular disease and/or diabetes, and/or eGFR < 60 mL/min/1.73 m², 1013 (48%) had BP ≥ 140/90 mmHg, and 1575 (75%) had BP higher than the recommended target for these participants of <130/80.11 An additional 253 participants receiving antihypertensive therapy were ≥75 years of age, without associated conditions or end-organ damage, of whom 167 (66%) had BP higher than the recommended target of <140/90.11

Antihypertensive drug classes

The number of antihypertensive drug classes received was similar for achieved BP levels of <140/90 mmHg, 140–159/90–99 mmHg and ≥160/100 mmHg (Table 2). Of 1092 men and 775 women with BP ≥ 140/90 mmHg, 856 men (78%) and 627 women (81%) were receiving only one or two antihypertensive drug classes, and the numbers receiving one drug class were higher than the numbers receiving two drug classes.

The most frequently prescribed antihypertensive drug class prescribed was angiotensin type 1 receptor blockers (ARB), with only small differences observed in the use of different drug classes between the different categories of achieved BP (Table 3). Moreover, the combination of ARB with thiazide/indapamide therapy was the most frequently prescribed combination of two drug classes, whereas the most frequent combination of three drug classes was ARB, thiazide/indapamide and calcium channel blocker, representing 7.3% of participants taking...
antihypertensive medication. Of the 3623 participants receiving antihypertensive therapy, 155 (4%) received loop diuretic therapy, which was not treated as antihypertensive therapy.

**Factors associated with BP ≥ 140/90 mmHg in participants receiving antihypertensive therapy**

Among participants receiving antihypertensive therapy, BP ≥ 140/90 mmHg was associated with age, male sex, waist circumference and log NT-proBNP (Table 4). By contrast, better BP control was observed in participants with self-reported ischaemic heart disease, atrial fibrillation and eGFR ≤ 60 mL/min/1.73 m² than without.

**Discussion**

SCREEN-HF study participants were volunteers aged ≥60 years with self-reported cardiovascular risk factors who were predominantly privately insured. Only half of those receiving antihypertensive therapy had BP < 140/90 mmHg despite two-thirds having high cardiovascular risk, and 80% of those with BP ≥ 140/90 were receiving only one or two antihypertensive drug classes. Thus, SCREEN-HF study participants achieved a level of BP control no better than that reported for the general Australian community.4,5 Our choice of BP as a measure of BP control was to allow comparison with previous Australian studies.4,5 This was a conservative measure of BP control because current guidelines recommend a target of <130/80 mmHg for individuals with ischaemic heart disease, diabetes, chronic kidney disease, moderate proteinuria (300–1000 mg/day) and cerebrovascular disease,11 although this target is subject to ongoing debate.12–14

We presented data for angiotensin converting enzyme (ACE) inhibitors and ARB as separate drug classes because although they both inhibit the renin angiotensin system, they act synergistically by different mechanisms.15 Moreover, 145 (4%) SCREEN-HF study participants receiving antihypertensive therapy were receiving both ACE inhibitor and ARB therapies, suggesting that clinicians may also regard them as separate drug classes.

While demonstrating considerable potential for improved prevention of cardiovascular and renal disease through better management of hypertension, our findings also suggest how BP control might be improved. Our data indicate a need for greater awareness of the guidelines for the management of hypertension in Australia.11

### Table 3 Classes of antihypertensive therapies prescribed

<table>
<thead>
<tr>
<th>BP category</th>
<th>ARB</th>
<th>ACE inhibitors</th>
<th>Thiazide/Indapamide</th>
<th>CCB</th>
<th>ß-blocker</th>
<th>Loop diuretic</th>
<th>Mineralocorticoid</th>
<th>Antagonist</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP &lt; 140 and DBP &lt; 90 mmHg</td>
<td>276 (21%)</td>
<td>217 (13%)</td>
<td>111 (9%)</td>
<td>31 (3%)</td>
<td>17 (1%)</td>
<td>3 (0%)</td>
<td>37 (3%)</td>
<td>0.8%</td>
<td>4%</td>
</tr>
<tr>
<td>SBP 140–159 and/or DBP 90–99 mmHg</td>
<td>125 (22%)</td>
<td>78 (14%)</td>
<td>75 (13%)</td>
<td>36 (6.4%)</td>
<td>55 (9.8%)</td>
<td>62 (11%)</td>
<td>101 (17%)</td>
<td>0.9%</td>
<td>4%</td>
</tr>
<tr>
<td>SBP ≥ 160 and/or DBP ≥ 100 mmHg</td>
<td>125 (22%)</td>
<td>78 (14%)</td>
<td>75 (13%)</td>
<td>36 (6.4%)</td>
<td>55 (9.8%)</td>
<td>62 (11%)</td>
<td>101 (17%)</td>
<td>0.9%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Data shown as number (%) of participants in each BP category. ARB, angiotensin type 1 receptor blockers; ACE, angiotensin converting enzyme; CCB, calcium channel blockers.

### Table 4 Multivariable logistic regression model for characteristics associated with systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg in SCREEN-HF study participants receiving antihypertensive therapy

<table>
<thead>
<tr>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.02 (1.01–1.04)</td>
</tr>
<tr>
<td>Male versus female</td>
<td>1.40 (1.20–1.61)</td>
</tr>
<tr>
<td>Log NT-proBNP (per log pmol/L)</td>
<td>1.34 (1.13–1.59)</td>
</tr>
<tr>
<td>Previous MI or other IHD versus none</td>
<td>0.68 (0.57–0.82)</td>
</tr>
<tr>
<td>Atrial fibrillation versus none</td>
<td>0.65 (0.51–0.83)</td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m² versus ≥60 mL/min/1.73 m²</td>
<td>0.71 (0.60–0.83)</td>
</tr>
<tr>
<td>Alcohol ≥2 drinks versus ≤ 2 drinks/day</td>
<td>1.19 (1.00–1.42)</td>
</tr>
<tr>
<td>Statin therapy versus none</td>
<td>0.94 (0.81–1.08)</td>
</tr>
<tr>
<td>Aspirin therapy versus none</td>
<td>0.89 (0.77–1.02)</td>
</tr>
<tr>
<td>NSAID therapy versus none</td>
<td>1.18 (0.93–1.49)</td>
</tr>
<tr>
<td>Waist circumference (per cm)</td>
<td>1.008 (1.002–1.014)</td>
</tr>
</tbody>
</table>

The logistic regression model included all variables in the table. eGFR, estimated glomerular filtration rate; IHD, ischaemic heart disease; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; NT-proBNP, amino-terminal-pro-B-type natriuretic peptide.
be controlled on one antihypertensive drug class and require combination therapy selected from two or more different drug classes. Current guidelines recommend that up to four antihypertensive drug classes be used in combination if necessary to achieve the target BP. Although compliance with prescribed antihypertensive drug therapy is a critical determinant of achieved BP and side effects may limit the number of antihypertensive drug classes that a patient can tolerate, implementation of these guidelines is likely to improve BP control in those individuals receiving only one or two drug classes. Guidelines from the European Society of Hypertension and from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommend combination of two antihypertensive drugs as the initial step in individuals with severe hypertension or an otherwise high-cardiovascular risk, and recent studies support this approach. Given the association between waist circumference and BP or smoking, although measured on a single occasion, and we did not control for control in Australia. The prevalence of BP to afford private health insurance. Our data can therefore in the SCREEN-HF study and who had sufficient income a group of individuals who were motivated to participate at least, our study provides information about BP control in Australia. The prevalence of BP ≥ 140/90 mmHg may have been over-estimated, as BP was measured on a single occasion, and we did not control for the use of stimulants such as recent caffeine consumption or smoking, although ≤4% of participants were current smokers. However, misclassification becomes less likely the higher the BP is above the threshold of 140/90 mmHg. and for more than half of SCREEN-HF participants receiving antihypertensive therapy the recommended target BP was <130/80 mmHg. Furthermore, Framingham study results have shown that maximum BP readings are as predictive of long-term cardiovascular outcomes as minimum or average BP values at screening. Moreover, for BP close to 140/90 mmHg, there was also the possibility of misclassification of BP < 140/90 mmHg. Self-reporting of antihypertensive drug use, comorbidities and lifestyle factors may have also been inaccurate, and we did not confirm medical histories. However, all SCREEN-HF study participants volunteered their participation and attended the physical examination, and information was obtained by ‘one-on-one’ interview by a study nurse.

Conclusion
Half of SCREEN-HF study participants receiving antihypertensive medication had BP ≥ 140/90 mmHg despite their high cardiovascular risk, and 79% of individuals with treated blood pressures above target received only one or two antihypertensive drug classes. Our data indicate considerable potential for prevention of cardiovascular and renal events in the Australian community through improved BP control by prescribing additional antihypertensive drug classes and lifestyle modification.

Acknowledgements
We are very grateful to Bupa Australia and to Sonia Danielewski (Bupa Australia) for their contribution to study recruitment, and to Dorevitch Pathology. We thank all SCREEN-HF study participants and the study nurses and administrative staff for their invaluable contribution.

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Hospitalisation of high-care residents of aged care facilities: are goals of care discussed?

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Key words
hospitalisation, nursing home, aged care facility, advance care planning, aged.

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Abstract
Background: Residents of residential aged care facilities (RACF) are commonly hospitalised towards the end of life. Determining the hospitalisation experiences, including the discussion of goals of treatment, is essential to best plan care including planning for end-of-life care for this population.

Aim: To document hospital presentation characteristics, course, outcomes and care planning for high-care residents of RACF.

Methods: A retrospective review of medical records was conducted for all high-care residents aged >64 years presenting to a metropolitan hospital over a 6-month period.

Results: One hundred and eighty-six high-care residents of RACF presented to hospital 228 times. Transfer paperwork documented resuscitation status for 49 (21%) presentations, and a medical enduring power of attorney or advanced care plan for 85 (37%). Patients had high rates of comorbidities (average Charlson comorbidity index score = 3), polypharmacy (93%), impaired mobility (89%), impaired cognition (81%) and incontinence (76%). Resuscitation status was documented in 50 (55%) and family discussion in 38 (42%) of 91 admissions exceeding 48 h. Documented family discussion was significantly associated with complications or new events occurring during admission (odds ratio 1.56, 95% confidence interval 1.07–2.26).

Conclusion: There were low rates of documentation of resuscitation status or family discussion for this highly vulnerable population. Neither hospitals nor community providers appear to take responsibility for future care planning. Acute hospitals could play a greater role in care planning because discussion around course of illness and goals of treatment may enhance patient management, satisfaction and reduce hospitalisations.

Introduction
In 2010 in Australia, there were 166 370 people living in residential aged care facilities (RACF),1 previously known as hostels and nursing homes. Fifty-five per cent were aged 85 years or older, and over one-quarter, 90 years of age or older.1 In the past decade, there has been an increase in the average age and care needs of people living in RACF, with 71% of residents requiring high care or ‘24-h nursing care’.1 For many, admission to a high-care bed in a RACF is due to chronic, life-limiting illness with dementia, in particular, being common (52%).1 The average length of stay in a RACF for both high-care and low-care residents is nearly 3 years.1 However, of those who die, one-quarter have been resident less than 6 months.1

Residents of RACF are often hospitalised, with 30 emergency department transfers for every 100 resident beds each year.2 These residents have a greater risk of functional decline, falls and death when hospitalised compared with community dwelling older people.3 Mortality rates of 7.8–10% for RACF residents presenting to an emergency department4,5 and 19% of those admitted to hospital are reported.4 Hospitalisation is common at the end of life, with 19–29% of resident deaths occurring in hospital and 41–58% of residents hospitalised at least once in the past 6 months of life.6,7 It has been estimated that 69% of RACF residents dying in hospital could have remained in the RACF to receive end-of-life care.8 A lack of experience and training in dealing with end-of-life issues has been identified by RACF staff as a factor contributing to transfers to the acute hospital.9 The institution of advanced care planning and end-of-life care programmes into RACF has resulted in reductions in hospitalisation of residents.10,11 This suggests that when
disease course and goals of care are discussed, some residents or their decision-making proxies choose to forego hospitalisation instead focusing on quality of life and symptom management in their RACF. As a result, advanced care planning and a palliative approach in residential aged care have been advocated.13,14

Current literature examining the hospitalisation of residents of RACF has commonly arisen from an emergency department perspective, with categorised presentations from RACF as ‘appropriate’ or ‘inappropriate’, as determined by retrospective medical opinion. According to these studies, between 8% and 44% of presentations to emergency department were ‘inappropriate’ and 67% ‘potentially avoidable’ if RACF were better resourced.16 The wide variation in results reflects the subjective nature of this outcome.

Little research has been undertaken examining hospitalisation experiences (including interventions and treatments) of high-care residents of RACF following admission, that is, beyond the emergency department. There are also scant data examining whether goals and resulting future treatment options are addressed. This study aims to examine the hospitalisation experience of high-care RACF residents by documenting the circumstances around hospital presentations, and the course and outcomes of admissions, with a particular focus upon whether advanced care planning and goals of care are discussed.

Methods

Design, setting and population

A retrospective review of medical records of patients aged 65 years or older residing in a high-care bed in a RACF and presenting to a metropolitan tertiary referral hospital between July 2009 and 1 January 2010 was conducted. All emergency department presentations, arranged admissions to inpatient wards and admissions to medical or surgical day units were included.

High-care patients were identified through the hospital’s electronic database by admission source coding where admission source was ‘Nursing Home’ or by hand search where the address was identified manually as a RACF with high care or ageing in place beds.

Data collection

Data collected from the medical record included:
1 Patient: demographical data, comorbidities (using the Charlson comorbidity index),19 geriatric syndromes (problems with cognition, mobility, continence, vision or hearing),20 polypharmacy (five or more regular medications or as required medications administered in the previous week),21 the number of documented admissions to any hospital and the number of days spent in the study hospital during the preceding 12 months.
2 Presentation: primary diagnosis, details of presentation, and information accompanying the patient upon transfer, including resuscitation status, enduring power of attorney, and/or an advanced care plan (defined as any documented wishes regarding future medical care beyond resuscitation status).
3 Course of hospital stay: for all presentations, interventions and treatments; for hospital admissions, longer than 48 h, complications and further medical events (occurring more than 48 h after admission), resuscitation status, and documented family discussions (including patient and other surrogate decision-makers).
4 Outcome: length of stay, discharge destination, and deaths.

Statistical analysis

Descriptive statistics were used to describe the sample. The primary outcome of interest, ‘family discussion documented’, was defined as a binary outcome. To examine the relationship between possible explanatory variables and documentation of a family discussion, t-tests, Fisher’s exact test and chi-squared analyses were conducted. Binary logistic regression was used to assess different possible explanatory variables of ‘family discussion documented’. Odds ratios (OR) and their associated 95% confidence intervals (CI) were calculated accordingly. Statistical analyses were considered significant at the 0.05 level. Statistical analyses were conducted using SPSS v18.0 (SPSS, Chicago, IL, USA).

This study was approved by the Institutional Human Research Ethics Committee.

Results

Sample

The final sample included 186 high-care residents of RACF with 228 hospital presenting during the study period. Of the 464 presenting to hospital during the study period, with an admission source of ‘Nursing Home’ or an address consistent with a RACF with high care or ageing in place beds, 248 were excluded because their care needs were low care (n = 188), they had moved into a RACF subsequent to the study period (n = 39), or they were in an independent living unit (n = 21). Others were excluded because they were transferred from respite care or another hospital (n = 13), their level of care was not documented (n = 13), or their notes were not located (n = 4).
Of the 186 high-care residents who had 228 separate presentations, the majority had single presentations (n = 156, 84%), with small numbers having two (n = 23, 12%), or three or more presentations to hospital (n = 7, 4%). In the 12 months prior to the study period, nearly half (n = 80, 43%) had been hospitalised, with a combined total of 148 hospital presentations.

Patient details

The average age of patients was 84.4 years (SD = 7.48). Patients originated from 23 countries, spoke 10 different preferred languages and resided in 67 different RACFs. Further patient demographics are shown in Table 1. Comorbidities were common (Table 2), and the average Charlson comorbidity index score was 3 (range 0–10),19 with dementia affecting more than two-thirds of patients (n = 129, 69%). Geriatric syndromes were also frequent (Table 2) but nevertheless still likely to be underrepresented because of lack of documentation of visual (n = 84, 45%), continence (n = 30, 16%) and cognitive problems (n = 24, 13%). Polypharmacy was almost universal (n = 173, 93%) with more than half (n = 100, 54%) taking 10 or more medications.

Presentation to hospital

Characteristics of the hospital presentations are shown in Table 3. Although most of those presenting to hospital had accompanying transfer documentation (n = 206, 90%), only a minority had documentation of resuscitation status (n = 49, 21%), or an enduring power of attorney or advanced care plan (n = 85, 37%) (Table 3). Of the 198 emergency department presentations, 81 (41%) were admitted to an inpatient ward, 59 (30%) to the emergency short-stay unit, and 52 (26%) were discharged back to their RACF. Three patients (1.5%) were transferred to another hospital, and three (1.5%) died in the emergency department.

Course of hospital stay

The procedures and treatments undertaken during the hospital visit are documented in Table 4. Ninety-one hospital presentations (40%) were longer than 48 h. Further events and complications for this group are included in Table 4.

Outcome of hospitalisation

The mean length of stay was 4.2 days (SD = 3.62) and ranged from 1 to 39 days. Of the 228 presentations to

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Table 1 Patient demographics (n = 186)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>65–74 years</td>
<td>21 (11)</td>
</tr>
<tr>
<td>75–84 years</td>
<td>70 (38)</td>
</tr>
<tr>
<td>85 or older</td>
<td>95 (51)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>111 (60)</td>
</tr>
<tr>
<td>Male</td>
<td>75 (40)</td>
</tr>
<tr>
<td>Country of birth</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>98 (53)</td>
</tr>
<tr>
<td>Italy</td>
<td>21 (11)</td>
</tr>
<tr>
<td>Greece</td>
<td>14 (8)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>43 (23)</td>
</tr>
<tr>
<td>Preferred language</td>
<td></td>
</tr>
<tr>
<td>English</td>
<td>147 (79)</td>
</tr>
<tr>
<td>Italian</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Greek</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Next of kin</td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td>100 (54)</td>
</tr>
<tr>
<td>Spouse</td>
<td>37 (20)</td>
</tr>
<tr>
<td>Sibling</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Niece/nephew, none and other</td>
<td>34 (18)</td>
</tr>
</tbody>
</table>

Table 2 Patient details: primary diagnoses, comorbidities and geriatric syndromes (186 patients with 228 presentations to hospital)

<table>
<thead>
<tr>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary diagnoses upon presentation (n = 228)</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Soft tissue injury or laceration</td>
</tr>
<tr>
<td>Arranged admission for minor procedure or investigation</td>
</tr>
<tr>
<td>Other infections</td>
</tr>
<tr>
<td>Fracture or dislocation</td>
</tr>
<tr>
<td>Falls, seizures and unresponsive episodes</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>CCF or COPD exacerbation</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Problem with PEG tube or urinary catheter</td>
</tr>
<tr>
<td>Other medical problems</td>
</tr>
<tr>
<td>Other surgical problems</td>
</tr>
<tr>
<td>Comorbidities of individuals (n = 186)</td>
</tr>
<tr>
<td>Dementia</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
</tr>
<tr>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>Hemiplegia</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Any tumour or malignancy</td>
</tr>
<tr>
<td>Geriatric syndromes of individuals (n = 186)</td>
</tr>
<tr>
<td>Mobility problems</td>
</tr>
<tr>
<td>Cognitive problems</td>
</tr>
<tr>
<td>Continence problems</td>
</tr>
<tr>
<td>Visual or hearing problems</td>
</tr>
<tr>
<td>Polypharmacy</td>
</tr>
</tbody>
</table>

CCF, congestive cardiac failure; COPD, chronic obstructive pulmonary disease; PEG, percutaneous endoscopic gastrostomy.
hospital, patients were generally discharged back to their RACF (n = 195, 86%), with small numbers discharged to an inpatient palliative care unit (n = 9, 4%), another hospital (private or regional) (n = 8, 4%) or other locations (n = 4, 2%). Twelve hospital presentations ended in death (5%), accounting for 6% of patients in the sample.

### Goals of care

Approximately half (n = 50, 55%) of the 91 patients admitted to hospital for longer than 48 h had a documented resuscitation status, including nine of 25 (36%) who underwent surgery. In all cases, documentation stated that the person was ‘not for resuscitation’, and all except one patient had some limitation on treatment placed, with the majority not for admission to intensive care (n = 49) and smaller numbers with further limitations including not for medical emergency team calls (n = 8).

In 38 (42%) admissions longer than 48 h, a discussion with family, or a surrogate decision-maker (n = 37) or patient (n = 1) was documented. The documentation of discussion with family was significantly related to having a greater number of new events or complications during the current admission (t = -2.32, d.f. = 89, P = 0.024) and with a longer length of stay (t = -3.36, d.f. = 89, P = 0.005), but not the number of previous admissions, Charlson comorbidity index, preferred language other than English, gender, or next of kin being a spouse or child (Table 5).

Pearson’s correlation analysis revealed that the variables, the number of new events or complications, and the length of stay were highly correlated (r = 0.55, P < 0.001). As the number of new events was predictive of the length of stay (rather than the other way around) and the number of new events or complications was clinically relevant to understanding predictors of a family discussion, the logistic regression was conducted with the variable new events or complications during the current admission. This revealed that a discussion around goals of care was more likely to occur with an increase in the number of complications or new events during the admission (OR 1.56, 95% CI 1.069–2.261), that is, with each new event or complication, the likelihood of a family meeting occurring increased by 1.56 times.

### Discussion

This study provides unique insights into the hospitalisation experience of high-care RACF residents, and the number and type of procedures or interventions they undergo. In particular, despite this being a highly vulnerable population and with high rates of comorbidities, the study reveals that advanced care planning is not undertaken routinely or proactively but instead only in response to complications or new events. These results are likely to be relevant to the broader high-care RACF population, as the sample in this study is likely to be representative given it had a similar age range and gender mix. The study group however had higher levels of cultural diversity than RACF residents Australia wide.
The development of complications from pneumonia and for those who develop a febrile illness may be contributing to the number of emergency department presentations. In this study, pneumonia (14%), a common event near the end of life with advanced dementia, was the most frequent reason for hospitalisation. Pneumonia can be anticipated and planned for and, if adequate resources are available, managed in a RACF with similar outcomes to hospital management. However, to facilitate this, care needs to be planned, and this starts with discussion of the prognosis of illnesses with patients and their families or surrogate decision-makers. Yet even though advanced care planning is recommended for all residents of RACF, only a minority of residents had a documented enduring power of attorney, advanced care plan or resuscitation status in their transfer documentation. When hospitalised, discussions with family or surrogate decision-makers and treatment limits were documented for a minority of patients despite many patients having multiple comorbidities, and dementia or cognitive impairment. Only the development of new problems or complications prompted care plans to be discussed with family. This finding is consistent with research comparing doctor and carer views about information exchange in an acute hospital. Doctors thought carers should be updated if there were a major change in the patient’s condition in contrast with carers who expected to receive information after every inpatient consultation. Unfortunately, this finding indicates that family discussions are conducted reactively and on an emergency basis rather than in an anticipatory fashion.

Perhaps, the lack of discussion with residents and family indicates that the acute services assume that such conversations are conducted by RACF staff and general practitioners. However, the low rates of documented advanced care plans, medical enduring power of attorney or resuscitation status in RACF transfer documentation suggest that these discussions are not occurring in the community despite their proven impact of reducing hospitalisation. A community outreach programme to educate and facilitate such discussions would face a number of challenges, considering patients in this study were cared for by multiple general practitioners and frequently spoke languages other than English. Perhaps acute care hospitals should assume a more active role in patient and family information provision and long-term care planning.

In order to provide optimal, coherent and consistent care for residents of aged care facilities moving between the community and hospital, attention should be paid to, and documentation made of the following: explanation of the natural history of major illnesses suffered, agreed goals and limits of care, key persons and decision-makers involved in care, and when possible, patient wishes. A systematic approach to ensure that these components of care are addressed and adequately communicated across care settings is required.

This study is limited by its retrospective nature and reliance on documentation contained in the medical record. Similarly, discussions with family or surrogate decision-makers may have been undertaken but not documented. However, discussions that clarify or change

### Table 5 Factors associated with the documentation of a family discussion

<table>
<thead>
<tr>
<th></th>
<th>Family discussion documented (n = 38) Mean (SD)</th>
<th>Family discussion not documented (n = 53) Mean (SD)</th>
<th>P-value</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>83.97 (6.12)</td>
<td>81.89 (8.04)</td>
<td>0.182</td>
<td>0.99, 5.17</td>
</tr>
<tr>
<td>Complications or new events during admission</td>
<td>1.34 (1.38)</td>
<td>0.74 (0.98)</td>
<td>0.024</td>
<td>0.08, 1.13</td>
</tr>
<tr>
<td>Length of stay</td>
<td>12.13 (10.57)</td>
<td>6.74 (4.25)</td>
<td>0.005</td>
<td>1.75, 9.04</td>
</tr>
<tr>
<td>Number of hospital admissions prior 12 months</td>
<td>1.03 (1.28)</td>
<td>1.19 (1.43)</td>
<td>0.579</td>
<td>0.42, 0.74</td>
</tr>
<tr>
<td>Number of days admitted to study hospital prior 12 months</td>
<td>6.63 (1.80)</td>
<td>5.76 (1.52)</td>
<td>0.718</td>
<td>0.41, 0.57</td>
</tr>
<tr>
<td>Number of prescribed medications</td>
<td>11.97 (4.79)</td>
<td>11.06 (4.96)</td>
<td>0.383</td>
<td>1.16, 2.99</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>3.38 (1.81)</td>
<td>3.50 (1.86)</td>
<td>0.753</td>
<td>0.65, 0.86</td>
</tr>
</tbody>
</table>

All factors analysed using independent samples t-tests. CI, confidence interval; SD, standard deviation.

The patients in this study had high rates of dementia. Dementia is a progressive and eventually fatal illness, with a 6-month mortality rate of 47–53% reported for people with advanced dementia who develop pneumonia and 45% for those who develop a febrile episode. The development of complications from dementia, such as aspiration pneumonia, frequently result in an acute deterioration in status and subsequent presentation to hospital. Hospital admission is therefore common and to a large degree may be anticipated. Previous research has found that when surrogate decision-makers have an understanding of the poor prognosis and clinical complications expected in advanced dementia, they are less likely to choose burdensome interventions, including hospitalisation. A lack of education about dementia among surrogate decision-makers in this population may be contributing to the number of emergency departments presentations.

In this study, pneumonia (14%), a common event near the end of life with advanced dementia, was the most frequent reason for hospitalisation. Pneumonia can be anticipated and planned for and, if adequate resources are available, managed in a RACF with similar outcomes to hospital management. However, to facilitate this, care needs to be planned, and this starts with discussion of the prognosis of illnesses with patients and their families or surrogate decision-makers. Yet even though advanced care planning is recommended for all residents of RACF, only a minority of residents had a documented enduring power of attorney, advanced care plan or resuscitation status in their transfer documentation. When hospitalised, discussions with family or surrogate decision-makers and treatment limits were documented for a minority of patients despite many patients having multiple comorbidities, and dementia or cognitive impairment. Only the development of new problems or complications prompted care plans to be discussed with family. This finding is consistent with research comparing doctor and carer views about information exchange in an acute hospital. Doctors thought carers should be updated if there were a major change in the patient’s condition in contrast with carers who expected to receive information after every inpatient consultation. Unfortunately, this finding indicates that family discussions are conducted reactively and on an emergency basis rather than in an anticipatory fashion.

Perhaps, the lack of discussion with residents and family indicates that the acute services assume that such conversations are conducted by RACF staff and general practitioners. However, the low rates of documented advanced care plans, medical enduring power of attorney or resuscitation status in RACF transfer documentation suggest that these discussions are not occurring in the community despite their proven impact of reducing hospitalisation. A community outreach programme to educate and facilitate such discussions would face a number of challenges, considering patients in this study were cared for by multiple general practitioners and frequently spoke languages other than English. Perhaps acute care hospitals should assume a more active role in patient and family information provision and long-term care planning.

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References


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POLG mutations in Australian patients with mitochondrial disease

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Key words
mitochondrial disease, POLG, DNA polymerase gamma, mitochondria, mitochondrial DNA.

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Abstract

Background/Aim: The nuclear POLG gene encodes the catalytic subunit of DNA polymerase gamma (polg), the only polymerase involved in the replication and proof-reading of mitochondrial DNA. As a consequence, POLG mutations can cause disease through impaired replication of mitochondrial DNA. To date, over 150 different mutations have been identified, with a growing number of associated phenotypes described. The aim of this study was to determine the prevalence of POLG mutations in an adult population of Australian patients with mitochondrial disease, displaying symptoms commonly associated with POLG-related diseases.

Methods: The clinical presentations of 322 patients from a specialist adult mitochondrial disease clinic were reviewed. Nineteen exhibited a cluster of three or more predefined clinical manifestations suggestive of POLG-related disease: progressive external ophthalmoplegia, seizures and/or an abnormal electroencephalogram, neuropathy, ataxia, liver function abnormalities, migraine or dysphagia/dysarthria. Patients were screened for mutations by direct nucleotide sequencing of the coding and exon-flanking intronic regions of POLG.


Conclusions: We conclude that the prevalence of pathogenic POLG mutations in our selected adult Australian cohort with suggestive clinical manifestations was 10%. A further 16% of patients had POLG variants but are unlikely to be responsible for causing their disease.

Introduction

The polymerase gamma gene (POLG or POLG1) is a nuclear gene that encodes the catalytic subunit of DNA polymerase γ (polγ). Polγ is the only polymerase present in mitochondria, where it is responsible for mitochondrial DNA (mtDNA) replication and repair and plays a major role in maintaining mtDNA integrity.1-3 Polγ is a trimeric protein complex composed of a catalytic subunit (POLG; encoded by the POLG gene) and a homo-dimer of accessory subunits (POLG2; encoded by the POLG2 gene).4-7 POLG has three functional domains: an amino-terminal 3′-5′ exonuclease domain for replication proof-reading; a carboxy-terminal polymerase domain for DNA replication; and a highly conserved spacer/linker region that interacts with the accessory POLG2 subunit.2,6,8-10

The POLG gene is a disease locus for several mitochondrial diseases, causing a wide range of neurological and muscular disorders with a variable age of onset and severity.9,11 Recent reviews of the clinical features of POLG-related diseases included an association between POLG mutations and Alpers disease, autosomal recessive and autosomal dominant progressive external ophthalmoplegia (arPEO and adPEO), and ataxia-neuropathy syndrome.12,11 Specific variants have also been associated
with valproate-induced hepatotoxicity alone\textsuperscript{14,15} or in the context of Alpers disease.\textsuperscript{16} With over 150 different mutations reported in \textit{POLG} to date (\textit{POLG} mutation database: http://tools.niehs.nih.gov/POLG/), there is suspicion that they are emerging as one of the most common causes of inherited mitochondrial disease, with estimates of up to 25\% of patients with mitochondrial disease having a \textit{POLG}-related disease (European Neuro Muscular Centre workshop).\textsuperscript{17,18}

Patients with \textit{POLG} mutations exhibit a wide spectrum of clinical phenotypes, adding to the challenge of diagnosing patients based on clinical symptoms. This phenotypic variability is likely a result of pathological mutations being spread across the different structural and functional domains of \textit{POLG}. Accurate diagnosis begins with the identification of DNA variants through direct sequencing of the \textit{POLG} gene.

The aim of this study was to determine the prevalence of \textit{POLG} mutations in a specialist adult Australian mitochondrial disease patient cohort exhibiting symptoms suggestive of \textit{POLG}-related disease.

\section*{Methods}

\section*{Patients}

The clinical symptoms of 322 patients presenting to a specialist mitochondrial disease clinic were reviewed. Patients were selected for \textit{POLG} screening if they had a cluster of three or more pre-defined clinical manifestations commonly associated with \textit{POLG}-related diseases.\textsuperscript{17,18} Nineteen patients exhibited three or more of the following clinical manifestations suggestive of \textit{POLG}-related disease: PEO, seizures or an abnormal electroencephalogram, peripheral neuropathy, ataxia, liver function abnormalities, migraine or dysphagia/dysarthria (Table 1).

\section*{POLG sequencing}

Ethics approval was obtained from the Northern Sydney Central Coast Human Research Ethics Committee and all study participants gave written informed consent. Whole blood samples were collected from the patients in a standard ethylenediaminetetraacetic acid-coated vacutainer tube. The buffy coat was collected for DNA extraction using the Promega Maxwell 16 Blood DNA purification kit (Promega Inc., Madison, WI, USA), according to the manufacturer’s instructions. Coding regions of the \textit{POLG} gene (exons 2–23 and intron/exon boundaries) were amplified by polymerase chain reaction (primer sequences: Table S1 with primers adapted from Wong \textit{et al}). Amplicons were sequenced by the Australian Genome Research Facility, Sydney, NSW, Australia, using the ABI BigDye terminator v.3.1 enzyme diodeoxy-terminator method (Applied Biosystems, Foster City, CA, USA) on an AB 3730xl machine. DNA sequences were

\begin{table}[h]
\centering
\caption{Clinical symptom selection criteria for the 19 selected patients}
\begin{tabular}{cccccccc}
\textbf{Patient} & \textbf{PEO} & \textbf{Seizures/EEG} & \textbf{Neuropathy} & \textbf{Ataxia} & \textbf{LFT change} & \textbf{Migraine} & \textbf{Dysphagia/dysarthria} \\
\hline
\#1 & ✓ & ✓ & ✓ & ✓ & ✗ & ✓ & ✓ \\
\#2 & ✓ & ✗ & ✓ & ✓ & ✓ & ✗ & ✓ \\
\#3 & ✓ & ✓ & ✓ & ✓ & ✗ & ✓ & ✓ \\
\#4 & ✗ & ✓ & ✓ & ✓ & ✓ & ✗ & ✓ \\
\#5 & ✗ & ✓ & ✓ & ✓ & ✗ & ✓ & ✓ \\
\#6 & ✓ & ✓ & ✓ & ✓ & ✓ & ✗ & ✓ \\
\#7 & ✗ & ✓ & ✓ & ✓ & ✓ & ✗ & ✓ \\
\#8 & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ & ✗ \\
\#9 & ✓ & ✓ & ✓ & ✓ & ✓ & ✗ & ✓ \\
\#10 & ✗ & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ \\
\#11 & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ \\
\#12 & ✗ & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ \\
\#13 & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ \\
\#14 & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ \\
\#15 & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ \\
\#16 & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ \\
\#17 & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ \\
\#18 & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ \\
\#19 & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ & ✓ \\
\hline
\end{tabular}
\end{table}

\textbf{Table 1} Clinical symptom selection criteria for the 19 selected patients

\textsuperscript{✓}, positive finding in patient; \textsuperscript{✗}, absent finding in patient; aura, migraine aura without headache; FHx, family history of seizures; PEO, chronic progressive external ophthalmoplegia; EEG abn, abnormal electroencephalogram without known clinical seizure; LFT, liver function tests; small fibre, isolated small fibre peripheral neuropathy.
aligned against the POLG reference sequence (ID NM_002693.1) using the Basic Local Alignment Search Tool function on the National Center for Biotechnology Information website and ChromasPro Version 1.5 (Technelysium, Helensvale, Qld, Australia). Identified variants were sequenced in both the forward and reverse directions.

**Results**

DNA samples from five of the 19 patients screened by sequencing were found to have informative POLG variants (patients #1–5 in Table 2). An informative variant is defined as a conserved amino acid in a patient exhibiting mitochondrial disease symptoms that may or may not have previously been shown to be pathological. The relative location of the identified variants within the POLG protein is shown in Figure 1. Informative variants are not necessarily pathogenic (i.e. causative of disease).

**Case studies**

Patient #1, a 21-year-old Caucasian woman, within hours of ingesting alcohol and the recreational drug benzylpiperazine (with euphoric and stimulant effects), developed right hemi-clonic seizures, progressing to refractory status epilepticus. She failed to respond to treatment with clonazepam and sodium valproate, the latter of which was ceased on suspicion of a mitochondrial condition. She was subsequently treated with phenytoin, carbamazepine, phenobarbitone and levetiracetam. She was the youngest of five siblings and her eldest brother had died at 6 years of age from an encephalitis of unknown cause with stroke-like episodes and cognitive decline. Cerebral magnetic resonance imaging (MRI) showed T2 hyperintensities in the parietal, occipital grey and white matter, the pre- and post-central gyri, associated with a large lactate peak on MR spectroscopy. Lactate levels were mildly elevated in both her cerebrospinal fluid (CSF) and serum, together with elevation of the CSF protein to 1.49 g/L.

Electroencephalogram showed slowing, and occipital epileptiform discharges. She continued to have recurrent hemi-clonic seizures despite increasing doses of antiepileptic medication. On examination, there was mild bilateral ptosis with external ophthalmoplegia, dysarthria, gaze-evoked nystagmus, with finger-to-nose dysmetria, cerebellar ataxia and a broad-based gait. She had isolated migratory myoclonus, predominantly involving the fingers, hands and head. She was areflexic, with decreased sensation to vibration and proprioception. Nerve conduction studies confirmed a sensorimotor peripheral neuropathy but normal electromyography. Her acute recovery period was complicated by bowel pseudo-obstruction and insulin resistance. The abnormalities on cerebral MRI resolved 10 months later, and she continued to make slow improvement, being able to walk without aid 2 years after her initial presentation. She continues to require multiple antiepileptic medications for optimal seizure control.

Patient #2, a 49-year-old woman, presented with increasing fatigue, and ongoing abdominal cramps, on a background of childhood-onset progressive sensorimotor peripheral neuropathy and symptoms of autonomic neuropathy with postural hypotension. Ptosis with proximal and distal myopathy, and gastrointestinal symptoms started in her early 40s, with severe diarrhoea alternating with constipation, an episode of megacolon and association with transient encephalopathy. On examination, there was bilateral ptosis, external ophthalmoplegia, facial weakness with palatal insufficiency and audible borborygmi. She had proximal and distal upper and lower limb weakness, with bilateral foot drop, and a sensory ataxia. She was areflexic with decreased pin-prick, proprioception and vibration sense distally. Investigations showed a mild elevation in serum lactate. Gastrointestinal transit studies showed diffuse colonic motility disorder. Cerebral MRI (fluid attenuated inversion recovery sequences) showed hyperintensity within the deep white matter bilaterally and mild involutional change. Nerve conduction studies showed a severe generalised sensorimotor peripheral neuropathy and electromyogram showed chronic neurogenic changes. Muscle biopsy of her left vastus lateralis showed a neuropathic process coupled with scattered atrophic, small angulated, ragged red and cytochrome oxidase (COX)-negative fibres.

Patient #3, a 34-year-old woman of Macedonian descent, left school in her mid-teens due to ill-health from ulcerative colitis and recurrent complex partial and generalised tonic clonic seizures. She had ongoing gastric and small bowel dysmotility after a colectomy and multiple admissions for recurrent pseudo-obstruction. She was noted to have diabetes on oral glucose tolerance test.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Nucleotide change</th>
<th>Amino acid change</th>
<th>Pathogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>c.487 C &gt; T</td>
<td>p.P163S</td>
<td>Heterozygous ?</td>
</tr>
<tr>
<td></td>
<td>c.2551 A &gt; G</td>
<td>p.T851A</td>
<td>Heterozygous Yes</td>
</tr>
<tr>
<td>#2</td>
<td>c.2551 A &gt; G</td>
<td>p.T851A</td>
<td>Heterozygous Yes</td>
</tr>
<tr>
<td></td>
<td>c.1402 A &gt; G</td>
<td>p.N468D</td>
<td>Heterozygous Yes</td>
</tr>
<tr>
<td>#3</td>
<td>c.2492 A &gt; G</td>
<td>p.Y831C</td>
<td>Heterozygous ?</td>
</tr>
<tr>
<td>#4</td>
<td>c.2492 A &gt; G</td>
<td>p.Y831C</td>
<td>Heterozygous ?</td>
</tr>
<tr>
<td>#5</td>
<td>c.1550 G &gt; T</td>
<td>p.G517V</td>
<td>Heterozygous ?</td>
</tr>
</tbody>
</table>
On examination, she had mild bilateral ptosis, ophthalmoparesis and gaze-evoked nystagmus. There was mild pigmentary retinopathy, sensorineural hearing loss and signs of palatal insufficiency. She had proximal myopathy involving the neck, shoulders and hip flexors. Cerebral MRI and spectroscopy found no structural abnormality, but an increased lactate peak was noted. Nerve conduction studies discovered a mild sensory peripheral neuropathy and myopathic features in the proximal muscles on electromyogram. The electroencephalogram showed mild slowing on several occasions. Her muscle biopsy showed a mild increase in intracellular lipid, without typical changes of mitochondrial myopathy seen on electron microscopy, and multiple mtDNA deletions were present in muscle.

Patient #4, a 46-year-old woman with no significant family history, presented with a background of classical migraine and intermittent palpitations, but no documented arrhythmia. She had onset of myokymic muscle twitches involving the face and hand muscles, which had not been evident on electromyogram. Muscle biopsy showed COX-negative fibres and subsarcolemmal aggregation of mitochondria on succinate dehydrogenase staining. No common mitochondrial point mutation or mtDNA deletion was identified. In the past 5 years, she has noticed increasing proximal weakness and myalgia, particularly post-exertion, requiring protracted periods to recover. She also described stereotypic symptoms of a feeling of warm water over her left foot, coinciding with twitches in her quadriceps that raised suspicion of an ictal phenomenon. Examination revealed mild asymmetrical ptosis and minimal proximal weakness. Reflexes were normal, as was coordination and sensation.

Patient #5, a 56-year-old woman, presented with a suspected mitochondrial myopathy based on her slowly progressive ataxia, dysarthria and dysphonia, youngonset asymmetrical sensorineural hearing loss, slow gastrointestinal transit times and proximal myopathy, where a single COX-negative fibre with mitochondrial disorganisation was noted on biopsy. Her mother had sensorineural hearing loss in her 60s, her son developed hearing loss before his early 20s and a maternal uncle had a history of seizures. Due to recurrent falls, she required a walking frame and was on a nocturnal continuous positive airway pressure machine for her obstructive sleep apnoea. Examination revealed evidence of palatal insufficiency and moderate dysarthria, but no obvious ptosis, facial weakness or proximal weakness. She had significant finger-nose ataxia and marked gait ataxia. Her electroencephalogram showed epileptiform features in the frontotemporal regions, without clinical seizures.

Discussion

We identified five informative POLG variants in our patients, with four of the variants having been previously reported in the literature (p.T851A, p.Y831C, p.N468D and p.G517V). A novel variant, p.P163S, was identified in a 21-year-old woman (patient #1) who presented with seizures and ataxia in compound heterozygosity with the known pathogenic variant p.T851A. The patient’s mother was heterozygous for the p.T851A variant, and her father was heterozygous for the p.P163S variant; however, neither parent exhibited clinical manifestations. The p.P163S variant is presumed to be pathogenic, arising as an autosomal recessive disorder requiring compound heterozygosity for disease expression.

The p.T851 residue is located in the pol palm 1 subdomain (Fig. 1) and has been shown to cause severely compromised polymerase activity resulting in little to no participation of the aberrant enzyme in mtDNA replication. The p.T851A variant is associated with DNA depletion in patients and hepatocerebral syndromes (mostly Alpers disease). However, patient #1 displayed an atypical phenotype inconsistent with Alpers disease, as she only exhibited seizures (one of the triad of clinical symptoms; seizures, psychomotor retardation and liver function abnormalities) and did not present in early childhood.
The p.P163 residue is located in the N-terminal domain between the polyglutamine tract and the exonuclease domain (Fig. 1) in an area of unknown function. At this stage, the pathogenicity of the p.P163S variant is unclear; however, proline has a high degree of evolutionary conservation in the organisms shown in Figure 2 (except *Saccharomyces cerevisiae*). The p.P163S variant was deemed to be novel, as it was not reported in the Human DNA *POLG* mutation database (http://tools.niehs.nih.gov/polg/) or the NCBI dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/index.html) and has not been published previously. The *POLG* mutation database also reports exhaustive exonc mutation screening in healthy control populations, providing further evidence that this variant is indeed novel.

Previous publications have identified *POLG* mutations in association with features of mitochondrial neurogastrointestinal encephalopathy (MNGIE).\(^1\) The symptoms displayed by patient #2 were consistent with defined clinical manifestations of *POLG* and MNGIE syndrome. *POLG* screening in patient #2 identified two variants, p.T851A and p.N468D. Similar to patient #1, this patient also did not have the typical presentation of Alpers disease commonly associated with the p.T851A variant. The other alteration, p.N468D, located in the pol thumb 1 subdomain (Fig. 1), has previously been associated with arPEO and sensory neuropathy.\(^{19,24-26}\) Both of which were evident in this patient.

The pathogenicity of the p.Y831C variant identified in patients #3 and #4, which is located in the pol palm 1 domain (Fig. 1), has been brought into question recently. Both of the patients described here exhibited features similar to those previously associated with p.Y831C, such as adPEO, neuropathy, hearing loss and proximal myopathy.\(^{27,28}\) However, the mother of patient #3 was also found to be heterozygous for the p.Y831C change and the father of patient #3 had no *POLG* mutations. Therefore, mother and daughter have the same *POLG* genotype but display markedly different phenotypes. Neither patient #3 nor her mother exhibited signs of Parkinsonism, features that have previously been reported with dominant expression of this variant.\(^{27,28}\) Moreover, it has been found at a high percentage in control populations, most notably in a Polish population (2.25%).\(^{29-31}\) The recent findings of Wong et al. and Tang et al. also indicate that p.Y831C is a neutral polymorphism even though its incidence in patients exhibiting symptoms suggestive of *POLG*-related diseases was high in these studies.

The pathogenicity of the final variant identified in this study, p.G517V (found in patient #5), is also under scrutiny. The p.G517V residue is located in the spacer region (Fig. 1) and has been commonly associated with the ataxia-neuropathy syndromes and adPEO.\(^{19,24,32,33}\) Both of which were evident in this patient. However, this variant has also been identified in control populations,\(^{19,32,34}\) it does not clearly segregate with a disease phenotype,\(^{17,19,35}\) and it has been demonstrated to have wild-type activity in vitro using a recombinant protein.\(^{36}\)

It is possible that patients who did not have any identifiable *POLG* mutations may have pathogenic variants within other genes, copy-number changes or large gene rearrangements that may contribute to the observed clinical phenotype. However, the literature reports that the occurrence of null mutations (~6%) and deletions/duplications (<1%) in *POLG* are relatively rare.\(^{35}\) Therefore, the Sanger DNA sequencing method used in this study is essentially capable of identifying the vast majority of mutated *POLG* alleles, as ~94% of all *POLG* mutations are missense changes.\(^{35}\)

While patient #1 did not develop significant hepatotoxicity from valproate as part of her treatment for seizures over 3 weeks, hepatotoxicity has been described to occur 2–3 months after commencement of treatment.\(^{34}\) The mutations identified in our patient were not those typically associated with valproate-induced hepatotoxicity. However, because we observed an exacerbation of seizure control in our patient, we suggest that any patient suspected of having a mitochondrial condition from *POLG* mutations should avoid treatment with sodium valproate.

**Conclusion**

In conclusion, 26% of the adult patients with mitochondrial disease displaying a phenotype suggestive of a *POLG*-related disease had ‘informative’ *POLG* coding variants identified in this study. Of these, only two patients...
were found to have conclusive pathogenic mutations segregating with symptoms indicative of POLG-related diseases (patient #1: p.T851A and p.P163S; patient #2: p.T851A and p.N468D). They displayed features of chronic progressive external ophthalmoplegia, seizures, neuropathy, ataxia and bulbar involvement. Because POLG-related diseases are phenotypically heterogeneous, it is difficult for clinicians to diagnose these diseases based solely upon a patient’s clinical phenotype. While POLG-related diseases are emerging as one of the most common causes of inherited mitochondrial disease,17,18 we agree with the proposal by Tang et al. that the POLG gene should be included as part of routine screening for mitochondrial diseases.

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Relapsed multiple myeloma: who benefits from salvage autografts?

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Royal Adelaide Hospital and SA Pathology, Adelaide, South Australia, Australia

Abstract

Background: Multiple myeloma is incurable despite the advance of autologous stem cell transplantation (ASCT) and novel agents (thalidomide, bortezomib, lenalidomide). The role of ASCT as salvage therapy in relapsed myeloma remains unclear.

Aim: To identify and refine the predictors of survival following salvage ASCT for relapsed multiple myeloma, so that they can be applied clinically for patient selection.

Methods: Retrospective review of patients treated salvage ASCT for relapsed myeloma at our centre from 1992 to 2011.

Results: Following an initial ASCT at diagnosis, 30 patients underwent salvage ASCT for subsequent relapse, with the median time to first relapse/progression being 30.2 months. All patients received reinduction, then melphalan-based conditioning with salvage ASCT. Non-relapse mortality at 100 days following salvage ASCT was 3%. The median overall survival and progression-free survival following salvage ASCT were 45 and 22 months respectively. The median progression-free survival following salvage ASCT was 4.2, 13.8 and 49.1 months respectively ($P < 0.0001$). The median overall survival was 10.7, 30.9 and 86.1 months respectively ($P < 0.0001$).

Conclusions: Salvage ASCT is an effective and safe treatment option in selected patients and should be considered in patients relapsing ≥36 months after their initial ASCT. The time-dependent relationship between PFI and salvage ASCT outcome is important when stratifying patient groups who may benefit from this procedure.
Introduction

Induction chemotherapy followed by high-dose therapy with autologous stem cell transplant (ASCT) is the current standard therapy for multiple myeloma in newly diagnosed patients who are transplant eligible. Additional benefits were observed with upfront tandem ASCT in some studies.\textsuperscript{1,2} Despite ASCT and novel agents, myeloma remains incurable and salvage therapy is required to prolong survival and maintain quality of life in patients with relapsed disease. There has been increasing interest in the role of ASCT in the relapsed setting. Retrospective studies of salvage ASCT have reported benefits, with the progression-free interval (PFI) after initial ASCT predictive of survival following salvage ASCT.\textsuperscript{3–8} However, the optimal predictive PFI cut-off varies between published studies, with many using single cut-off points only.\textsuperscript{5,6,8}

The PFI following initial therapy is influenced by the biology of the underlying myeloma clone and effectiveness of therapy and is a spectrum rather than a single defining point. The decision in the selection of relapsed patients for salvage ASCT remains subjective.

In this retrospective analysis, we reported the predictors of survival following salvage ASCT for relapsed multiple myeloma. Furthermore, we aimed to refine the PFI to increase its clinical applicability.

Method

We reviewed the medical records of all myeloma patients who underwent salvage ASCT from January 1992 to January 2011 at the Royal Adelaide Hospital. Salvage ASCT refers to ASCT performed for patients who relapsed following an initial ASCT. Patient selection for salvage ASCT was an individualised process based on a combination of patient preferences, age, performance status, organ function, stem cells availability, access to and response with other treatment options, and clinicians’ judgement.

Patients who underwent autologeneic transplants at relapse were excluded. Collection and analysis of the data was approved by the hospital’s Research Ethics Committee. Response status to therapy was assessed using the International Myeloma Working Group criteria.\textsuperscript{9}

Potential covariates identified for analysis included age, international staging system (ISS), paraprotein subtype, PFI post-initial ASCT, responses to reinduction and ASCT, use of novel agents, and maintenance therapy post-salvage ASCT. Cytogenetic data were collected where available.

Progression-free survival (PFS) and overall survival (OS) were derived using the Kaplan–Meier method and log-rank tests. All calculations were performed using SAS Version 9.2 (SAS Institute, Inc., Cary, NC, USA) and SPSS 19.0 (SPSS, Inc., Chicago, IL, USA).

Results

During the study period, 292 patients underwent initial ASCT for newly diagnosed multiple myeloma. Salvage ASCT was performed in 30 patients. Table 1 details the baseline characteristics of these 30 patients during the initial transplant period. Stem cells were harvested after cyclophosphamide (3–7 g/m\textsuperscript{2}) and granulocyte-colony stimulating factor (G-CSF) in 27 patients. One patient was mobilised after combination of dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide,\textsuperscript{10} and two patients were mobilised with G-CSF only. Our approach was to collect sufficient stem cells for two transplants, especially in younger patients. Following initial ASCT, 18 patients achieved at least a very good partial response (VGPR), and 11 patients achieved partial

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics at initial ASCT (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>International staging system (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>53</td>
</tr>
<tr>
<td>II</td>
<td>33</td>
</tr>
<tr>
<td>III</td>
<td>13</td>
</tr>
<tr>
<td>% Male</td>
<td>43.3</td>
</tr>
<tr>
<td>Median age at diagnosis (range)</td>
<td>55 [31–70]</td>
</tr>
<tr>
<td>Paraprotein subtype (%)</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>50</td>
</tr>
<tr>
<td>IgA</td>
<td>27</td>
</tr>
<tr>
<td>IgD</td>
<td>3</td>
</tr>
<tr>
<td>Light chain</td>
<td>13</td>
</tr>
<tr>
<td>Non-secretory</td>
<td>7</td>
</tr>
<tr>
<td>Induction therapy at initial diagnosis (%)</td>
<td></td>
</tr>
<tr>
<td>VAD</td>
<td>77</td>
</tr>
<tr>
<td>Thalidomide containing (DT-PACE or DT)</td>
<td>10</td>
</tr>
<tr>
<td>VAMP</td>
<td>10</td>
</tr>
<tr>
<td>CID</td>
<td>3</td>
</tr>
<tr>
<td>Conditioning for initial ASCT</td>
<td></td>
</tr>
<tr>
<td>Melphalan only (200 mg/m\textsuperscript{2})</td>
<td>n = 21</td>
</tr>
<tr>
<td>Melphalan + TBI</td>
<td>n = 5</td>
</tr>
<tr>
<td>Busulfan and melphalan</td>
<td>n = 3</td>
</tr>
<tr>
<td>Melphalan only (140 mg/m\textsuperscript{2})</td>
<td>n = 1</td>
</tr>
<tr>
<td>Median PFI after initial ASCT</td>
<td>30.2 m (4–187)</td>
</tr>
<tr>
<td>PFI &lt; 18 months</td>
<td>n = 5</td>
</tr>
<tr>
<td>PFI 18–36 months</td>
<td>n = 13</td>
</tr>
<tr>
<td>PFI &gt; 36 months</td>
<td>n = 12</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplant; CID, cyclophosphamide, idarubicin, dexamethasone; DT, dexamethasone, thalidomide; DT-PACE, DT cisplatin, doxorubicin, cyclophosphamide and etoposide; Ig, immunoglobulin; PFI, progression-free interval; TBI, total body irradiation; VAD, vincristine, adriamycin, dexamethasone; VAMP, vincristine, adriamycin, methylprednisolone.
First-line salvage reinduction (multiple lines in some) P
reinduction to 27% post-salvage ASCT (tion of patients inVGPR improved from 7% post-salvage
158
of cotrimoxazole prophylaxis. from pneumocystis pneumonitis after completing a year
other patient died 13 months following salvage ASCT
in our institute’s conditioning regimen for myeloma. The
liver dysfunction from busulphan related veno-occlusive
patient died on day 68 post-salvage ASCT, with acute
post-salvage ASCT were 3% and 7% respectively. One
ASCT, the median PFS was 22 months and median OS 45
Table 3 categorises the number of patients by response
(10% (n = 3)).
Lines of reinduction
1
n = 15
2
n = 12
≥3
n = 3
Conditioning for salvage ASCT
Melphan (200 mg/m²)
n = 19
Melphan (200 mg/m²) + bortezomib
n = 1
Busulfan and melphalan
n = 3
Reduced-dose melphalan (100–140 mg/m²)
n = 7
Timing of stem cell collection
Prior to initial ASCT 90% (n = 27)
Remobilised after relapse 10% (n = 3)
Maintenance post-salvage ASCT 67%
ASCT, autologous stem cell transplant; CTD, cyclophosphamide, thalido-
mide, dexamethasone; DT, dexamethasone, thalidomide; DT-PACE, DT cis-
platin, doxorubicin, cyclophosphamide and etoposide; VAD, vincristine,
adriamycin, dexamethasone.
response (PR). The median PFI after the initial ASCT was
30.2 months. Two patients relapsed within 12 months.
At relapse, VAD was used as a reinduction regimen in
nine patients (Table 2). Fifteen patients had two or more
lines of reinduction therapy, and novel agents were used
in 16 patients. Twenty-seven patients had sufficient stem
cells collected prior to their initial ASCT, and three
patients required remobilisation. All patients had melphalan-based conditioning (Table 2).
Following salvage ASCT, the overall response rate
(complete response + VGPR + PR) was 80%. The propor-
tion of patients in VGPR improved from 7% post-salvage
reinduction to 27% post-salvage ASCT (P = 0.0082).
Table 3 categorises the number of patients by response
status following initial ASCT, salvage reinduction and
salvage ASCT.
With a median follow-up of 32 months after salvage
ASCT, the median PFS was 22 months and median OS 45
months. Non-relapse mortality at 100 days and 2 years
post-salvage ASCT were 3% and 7% respectively. One
patient died on day 68 post-salvage ASCT, with acute
liver dysfunction from busulphan related veno-occlusive
disease used in conditioning. Busulphan is no longer used
in our institute’s conditioning regimen for myeloma. The
other patient died 13 months following salvage ASCT
from pneumocystis pneumonia after completing a year
of cotrimoxazole prophylaxis.
The most significant finding was the observation of
progressively longer median PFS and OS following salvage
ASCT, with increasing PFI after initial ASCT. Utilising PFI
cut-offs of under 18 months, 18–36 months and more
than 36 months, the median PFS following salvage ASCT
was 4.2, 13.8 and 49.1 months respectively (P < 0.0001, Fig. 1a). The median OS was 10.7, 30.9 and 86.1 months
respectively (P < 0.0001, Fig. 1b). Single PFI cut-offs of 18,
24 and 36 months also demonstrated statistically signifi-
cant differences in PFS after salvage ASCT (Table 4).
Analysis of other potential factors confirmed that the
ISS at diagnosis was also associated with survival benefit
after salvage ASCT (P = 0.0063 for OS). However, use of
novel agents in reinduction, maintenance therapy and
response status post-salvage ASCT did not influence PFS
following salvage ASCT (P = 0.651, P = 0.453, P = 0.541
for PFS respectively). Cytogenetic data were available for
only one third of the patients and hence were not
included in the analysis.
Discussion
In this single institutional experience, we found that
selected patients with relapsed myeloma achieved a
median OS of 45 months following salvage ASCT. Our
survival and mortality outcomes compared favourably
with published studies, with reported median OS after
salvage ASCT ranging from 19 to 53 months. In these
studies, the median PFS following salvage ASCT ranged
from 8.5 to 16.43 months compared with 22 months in
our study. Our non-relapse mortality at day 100 of 3%
was also comparable with those in recent published
studies of 2.6–8%. Importantly, our study suggested
that the PFI after the initial ASCT predicted the PFS and
OS following salvage ASCT. These findings are in accord-
ance with previously published studies. Various PFI
cut-offs have been reported ranging from 9 months to 24
months.

Table 2 Patient characteristics at salvage ASCT (n = 30)

<table>
<thead>
<tr>
<th>Median age at salvage ASCT (range)</th>
<th>59 (34–73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line salvage reinduction (multiple lines in some)</td>
<td></td>
</tr>
<tr>
<td>VAD</td>
<td>n = 9</td>
</tr>
<tr>
<td>Thalidomide-containing (CTD, DT, DT-PACE)</td>
<td>n = 14</td>
</tr>
<tr>
<td>Bortezomib-containing</td>
<td>n = 1</td>
</tr>
<tr>
<td>Lenalidomide-containing</td>
<td>n = 1</td>
</tr>
<tr>
<td>Melphalan-containing</td>
<td>n = 3</td>
</tr>
<tr>
<td>Other</td>
<td>n = 2</td>
</tr>
<tr>
<td>Lines of reinduction</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>n = 15</td>
</tr>
<tr>
<td>2</td>
<td>n = 12</td>
</tr>
<tr>
<td>≥3</td>
<td>n = 3</td>
</tr>
<tr>
<td>Conditioning for salvage ASCT</td>
<td></td>
</tr>
<tr>
<td>Melphan (200 mg/m²)</td>
<td>n = 19</td>
</tr>
<tr>
<td>Melphan (200 mg/m²) + bortezomib</td>
<td>n = 1</td>
</tr>
<tr>
<td>Busulfan and melphalan</td>
<td>n = 3</td>
</tr>
<tr>
<td>Reduced-dose melphalan (100–140 mg/m²)</td>
<td>n = 7</td>
</tr>
<tr>
<td>Timing of stem cell collection</td>
<td></td>
</tr>
<tr>
<td>Prior to initial ASCT</td>
<td>90% (n = 27)</td>
</tr>
<tr>
<td>Remobilised after relapse</td>
<td>10% (n = 3)</td>
</tr>
<tr>
<td>Maintenance post-salvage ASCT</td>
<td>67%</td>
</tr>
</tbody>
</table>

Table 3 Response status following initial ASCT, salvage reinduction and salvage ASCT in study cohort (n = 30)

<table>
<thead>
<tr>
<th>Response status</th>
<th>Post-initial ASCT</th>
<th>Post-salvage reinduction</th>
<th>Post-salvage ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGPR+</td>
<td>n = 18</td>
<td>n = 2</td>
<td>n = 8</td>
</tr>
<tr>
<td>PR</td>
<td>n = 11</td>
<td>n = 19</td>
<td>n = 16</td>
</tr>
<tr>
<td>SD</td>
<td>n = 1</td>
<td>n = 8</td>
<td>n = 5</td>
</tr>
<tr>
<td>PD</td>
<td>n = 0</td>
<td>n = 1</td>
<td>n = 0</td>
</tr>
</tbody>
</table>

One patient died at day 68 post-salvage ASCT; hence, restaging was not performed. ASCT, autologous stem cell transplant; PD, progressive
disease; PR, partial response; SD, stable disease; VGPR+, very good partial response and above.

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The more significant finding is a time-dependent relationship between the length of PFI and survival after salvage ASCT. This suggests that using a single PFI cut-off as a selection criterion will have limitations because it implies that patient selection is a simple yes/no decision. Instead, clinical decisions can include identifying those for whom a salvage autograft is considered inadvisable, those for whom a salvage autograft is definitely worth considering and an intermediate group where other factors are more strongly considered.

In general, patients will require 3–6 months for full recovery after an ASCT. In those with PFI of less than 18 months, the median PFS following salvage ASCT is only 4.2 months, inferring that they are likely to relapse again before they recover from their salvage ASCT. Therefore, salvage ASCT should not be offered to these patients (PFI < 18 m). Most centres no longer offer salvage ASCT to patients who relapse within 12 months after initial ASCT because of their inferior outcomes.4,6,11

On the other hand, if a patient relapses more than 36 months after their initial ASCT (PFI > 36 months), salvage ASCT produces a clinically beneficial outcome with a median 49.1 months PFS.

In patients with PFI between 18 and 36 months, the median PFS is 13.8 months; thus, the decision to salvage transplant in these patients would be more dependent on other factors including availability of alternative therapies. A proposed algorithm is shown in Figure 2.

Tables 3 and 4 reinforce the general observation that multiple myeloma becomes increasingly more difficult to treat with subsequent relapses, as evident by the decreasing duration of remission and lower rates of VGPR with salvage treatments.

**Conclusion**

Despite the limited sample size, retrospective methodology and the time period of our study, our results are

![Figure 1](image-url)  
**Figure 1** (a) Progression-free survival after salvage autologous stem cell transplant (ASCT) – effect of progression-free interval (PFI) after initial transplant. (b) Overall survival after salvage ASCT – effect of PFI after initial transplant. (——), PFI 18–36 months; (—··—·), PFI < 18 months; (——), PFI > 36 months.

**Table 4** Median progression-free survival (PFS) after salvage ASCT using different PFI cut-offs

<table>
<thead>
<tr>
<th>PFI cut-offs (months)</th>
<th>n</th>
<th>P value (log-rank)</th>
<th>Median PFS after salvage ASCT (median time to first progression/relapse after initial ASCT) (months)</th>
<th>95% CI of median PFS after salvage ASCT (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>5</td>
<td>0.000</td>
<td>4.2</td>
<td>2.6–5.8</td>
</tr>
<tr>
<td>&gt;18</td>
<td>26</td>
<td></td>
<td>28.2</td>
<td>18.2–38.1</td>
</tr>
<tr>
<td>&lt;24</td>
<td>11</td>
<td>0.002</td>
<td>7.9</td>
<td>2.3–13.4</td>
</tr>
<tr>
<td>&gt;24</td>
<td>19</td>
<td></td>
<td>31.0</td>
<td>17.7–44.3</td>
</tr>
<tr>
<td>&lt;36</td>
<td>18</td>
<td>0.000</td>
<td>12.6</td>
<td>5.9–19.3</td>
</tr>
<tr>
<td>&gt;36</td>
<td>12</td>
<td></td>
<td>49.2</td>
<td>37.4–60.9</td>
</tr>
<tr>
<td>&lt;18 18–36</td>
<td>5</td>
<td>0.000</td>
<td>4.2 (12.7)</td>
<td>2.6–5.8</td>
</tr>
<tr>
<td>18–36</td>
<td>13</td>
<td></td>
<td>13.8 (24.2)</td>
<td>12.0–15.5</td>
</tr>
<tr>
<td>&gt;36</td>
<td>12</td>
<td></td>
<td>49.2 (57.8)</td>
<td>37.4–60.9</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplant; CI, confidence interval; PFI, progression-free interval after initial ASCT.

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First relapse after initial ASCT

Transplant eligible?
- Age
- Performance status
- Organ function

YES

Progression-free interval after initial ASCT

<18 months
Salvage ASCT not recommended

18–36 months
Reinduction with novel agent-based chemotherapy

>36 months
Reinduction with novel agent-based chemotherapy

NO
Non-transplant salvage therapies

# Decision to consolidate with salvage ASCT would also depend on the following factors:
- Stem cell availability (and ease of remobilisation if required).
- Patient preference (experience and toxicities with initial ASCT).
- Availability and side-effects of other therapies and clinical trials.

Consolidation with salvage ASCT can be considered if no alternative treatments available #

Consolidation with salvage ASCT recommended #

Figure 2 Proposed algorithm for patient selection in salvage autologous stem cell transplant (ASCT) for relapsed myeloma.
consistent with previously published studies on salvage autografts. In contrast with most published literature, this study utilised more than one cut-off point of PFI after initial ASCT. Prospective studies of transplant-eligible relapsed patients randomised to salvage ASCT or alternative therapies would help to confirm our findings and clarify the role of salvage ASCT in the era of novel agents.

With increasing availability of new agents, salvage ASCT may become less attractive. However, until a cure is found for myeloma, all potential treatment options should be considered in patients with relapses. Salvage ASCT may augment the responses from novel agents and can achieve durable responses in selected patients. Application of graded PFI categories rather than a single PFI cut-off may improve precision in patient selection for this salvage option.

Acknowledgements
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References
Shorter preparation to procedure interval for colonoscopy improves quality of bowel cleansing

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Key words
colonoscopy, bowel preparation, polyp.

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Abstract

Background: The timing of bowel preparation for colonoscopy influences the quality of bowel cleansing and the success of the procedure.

Aim: We aimed to determine whether the interval between the end of bowel preparation and the start of colonoscopy influences preparation quality.

Methods: We retrospectively analysed 1785 colonoscopies performed between January 2010 and January 2011. The quality of bowel cleansing was compared between those who had a less than 8-h interval between the end of bowel preparation to the start of the procedure versus those who had a greater than 8-h interval. Univariate and multivariate logistic regression analyses evaluated quality of bowel cleansing, preparation to procedure time, age, gender, hospital inpatient or outpatient status, indication for colonoscopy, caecal intubation rate, and segmental polyp detection.

Results: Fifty-three per cent of the cohort was male. Eighty-nine per cent were outpatients. Bowel cleansing was reported as satisfactory/good in 87% and poor in 13%. A <8-h preparation to procedure time was associated with a higher rate of satisfactory/good cleansing than a >8-h interval (odds ratio (OR) 1.3, \(P = 0.04\)). In a multivariate analysis, female gender (OR 1.4, \(P = 0.02\)), outpatient status (OR 3.1, \(P = 0.001\)) and indication for procedure (\(P < 0.01\)) were significant predictors of adequate bowel preparation. Adequate bowel preparation was associated with a significant increase in caecal intubation rates (OR 5.3, \(P = 0.001\)).

Conclusions: A shorter (<8 h) interval between end of bowel preparation and start of colonoscopy yielded better bowel cleansing than a longer (>8 h) interval. Adequate bowel preparation led to improved caecal intubation rates.

Introduction

Colonoscopy has an established role in the early detection and prevention of colorectal cancer and has been implemented as a part of bowel cancer screening programmes.\(^1\)\(^-\)\(^3\) Adequate bowel preparation for colonoscopy is essential to achieve adequate visualisation of the colonic mucosa. Poor bowel preparation leads to decreased caecal intubation rates, decreased adenoma detection rates,\(^4\)\(^-\)\(^5\) prolonged procedure times\(^6\) and a higher risk of complications.\(^7\)\(^-\)\(^8\) The cost burden of poor bowel preparation for colonoscopy is also significant.\(^9\)

Predictive factors for inadequate bowel preparation for colonoscopy include patient factors such as older age, female gender and non-compliance with bowel preparation.\(^10\)\(^-\)\(^11\) The timing of the procedure has previously been shown to be of importance, with higher failure rates and lower adenoma detection rates for afternoon procedures.\(^12\)\(^-\)\(^14\) However, the timing of administration of bowel preparation has emerged as a more significant factor in the quality of bowel preparation than the timing of the procedure. A shorter interval between end of ingestion of bowel preparation and the start of colonoscopy has been associated with better bowel cleansing in several recent studies.\(^14\)\(^-\)\(^16\) Accordingly, the quality of bowel preparation for afternoon procedures is significantly improved by administration of bowel preparation on the morning of the procedure day.\(^17\)\(^-\)\(^18\) A shorter preparation to procedure interval is the likely factor belying the efficacy of ‘split’ bowel regimens, which have been recommended as the preferred cleansing method in recent colorectal cancer screening guidelines.\(^19\)\(^-\)\(^22\)

We sought to analyse the factors influencing the quality of bowel cleansing for colonoscopies performed in a single large Australian centre, in particular, the impact
of a shorter interval between ingestion of bowel preparation and the start of colonoscopy. We then sought to assess the outcomes of colonoscopy with regard to caecal intubation and segmental polyp detection rates relative to the quality of bowel preparation.

Methods

This is a retrospective observational study analysing factors influencing quality of bowel preparation and colonoscopy outcomes in a large single-centre cohort. Data were gathered on all consecutive colonoscopies performed at the Royal Adelaide Hospital, Adelaide, South Australia between 1 January 2010 and 31 December 2010 using an endoscopy database by the corresponding author without additional case note review. All colonoscopies performed in the period were analysed. Excluded from the final analysis were colonoscopies performed in patients with a prior history of large bowel resection, colonoscopies where caecal intubation could not be achieved due to an obstructing lesion, and colonoscopy reports which did not report on bowel preparation.

Information was obtained from the colonoscopy report on patient demographics including age and gender. The indication for procedure was recorded as stated on the colonoscopy report. The indications were grouped as screening and surveillance, colitis, anaemia and rectal bleeding, altered bowel habit, abdominal pain, and other (including diverticulosis, weight loss, investigation for primary malignancy and cases where the indication was not documented). The inpatient or outpatient hospital status at the time of the procedure was obtained from the report. The time of procedure was ascertained, with a morning procedure classified as one occurring between 8:30am and 12:30pm, and an afternoon procedure between 1:00pm and 4:30pm.

The quality of bowel cleansing was assessed as documented on the colonoscopy report. This was a subjective contemporaneous scale recorded by the endoscopist at the time of the procedure. Overall, bowel cleansing quality was classified according to the preset scale set out in the database as either poor, satisfactory or good. Bowel preparation quality was then grouped poor versus satisfactory or good for subsequent analysis.

The extent of colonoscopic examination was ascertained from the colonoscopy report. Extent of examination was dichotomised as achieving caecal intubation or not. Caecal intubation was defined as identification of at least two features of the caecal pole: the ileocaecal valve, tri-radiate fold, appendiceal orifice or transillumination. Data on polyp detection were gathered from the colonoscopy report. The findings of polyp/s overall were then recorded and then classified as right colonic (proximal to the splenic flexure) and left colonic (including and distal to the splenic flexure).

Bowel preparation regimens were either polyethylene glycol (PEG) (Colonlyte, Dendy Pharmaceuticals Australia Pty Ltd, Melbourne, Vic., Australia) alone, or PEG in combination with sodium picosulphate (Picoprep, Fresenius Kabi Australia Pty Ltd, Sydney, NSW, Australia). For afternoon procedures (performed between 1:00pm and 4:00pm), the interval between completion of ingestion of bowel preparation and the start of the colonoscopy was less than 8 h (5–7.5 h). The bowel preparation was split (given on the day prior to and on the day of the procedure). The PEG-only preparation regimen involved consuming 2 L of solution the day prior to the procedure (between 5:00pm and 7:00pm) and a further 2 L of solution on the morning of the procedure (prior to 8:00am). The combination preparation regimen involved two sachets of sodium picosulphate on the day prior to the procedure (at 1:00pm and 5:00pm), and the 1-L PEG consumed on the morning of the procedure (prior to 8:00 am).

For morning procedures (performed between 8:30am and 12:30pm), the interval between the completion of ingestion of bowel preparation and the start of the colonoscopy was more than 8 h (8.5–17 h). The bowel preparation was administered the day prior to the procedure. The PEG-only preparation involved consuming 4 L of solution between 2:00pm and 7:00pm on the day prior to procedure or combination preparation that involved consuming two sachets of sodium picosulphate on the day prior to the procedure at 9:00am and 1:00pm, and 1 L of PEG at 4pm.

Before the procedure, written information was provided to all patients regarding the bowel preparation protocol by scheduling staff. Patients were instructed to eat a low-residue diet 2 days prior to the procedure and to take only clear fluids 1 day prior to the procedure. Patients were advised to fast for 4–6 h prior to commencement of the procedure.

Colonoscopies were performed by consultant gastroenterologists or by registrars or Fellows under supervision. Colonoscopies were performed with either sedation administered by the proceduralist using fentanyl and midazolam, or under propofol sedation administered by an anaesthetist.

Statistical analysis was performed using SAS software package Version 9.2 (SAS Institute, Inc., Cary, NC, USA). The variables were established a priori: preparation to procedure time, patient age as grouped into a categorical predictor in three levels (age <55 years, 55–69 years, or 70 or older), patient gender, inpatient or outpatient hospital status, and indication for procedure (grouped as set
out earlier). A logistic regression model was fitted to the data adjusted for the covariates constituting a multivariate analysis. A univariate logistic regression analysis model was applied to assess quality of bowel preparation as dichotomised into poor versus satisfactory/good as a predictor of caecal intubation, polyt detection overall, and right- and left-sided polyt detection. Results of univariate and multivariate analyses are presented as odds ratios (OR). Statistical significance was defined as \( P < 0.05 \).

The study was conducted in accordance with Royal Adelaide Hospital Ethics Committee guidelines, with strict adherence to confidentiality and the ethical principle of respect for the participant. The participant information was accordingly stored in a depersonalised manner.

**Results**

A total of 1917 colonoscopies was analysed. Excluded were 71 with a history of prior large bowel surgery, 34 where an obstructing lesion preventing progress and 27 where the quality of bowel preparation was not reported. The remaining 1785 colonoscopies were included in the statistical analysis. As shown in Table 1, the overall bowel preparation quality was satisfactory or good for 1557 (87\%) colonoscopies analysed and poor for 228 colonoscopies (13\%).

As shown in Table 1, multivariate analysis adjusting for covariates of age, gender, admission status and indication for colonoscopy revealed that a shorter preparation to procedure time (<8 h) for afternoon procedures was a significant predictor of satisfactory/good bowel preparation compared with a longer preparation to procedure time (>8 h) for morning procedures (OR 1.3, confidence interval (CI) 1.008–1.8, \( P = 0.04 \)).

Multivariate analysis controlling for variables (age, gender, inpatient or outpatient status, preparation to procedure time, and indication for procedure) as predictors of bowel preparation quality are shown in Table 2. Gender was shown to be a modest but significant predictor of the quality of bowel cleansing, with female gender a significant predictor of satisfactory/good preparation (OR 1.4, CI 1.046–1.8, \( P = 0.02 \)). Age was not a significant predictor of the quality of bowel preparation either as a categorical variable (as presented with \( P = 0.84 \)) or as a continuous variable (not presented).

Inpatient or outpatient status was shown to be a very significant predictor of quality of bowel cleansing. Outpatient status was a significant predictor of satisfactory/good preparation as shown in Table 2 (OR 3.1, CI 2.1–4.3, \( P < 0.0001 \)). Bowel preparation in inpatients was frequently poor (27\% of inpatients).

As shown in Table 2, the indication for colonoscopy was a significant predictor of bowel cleansing quality overall (\( P = 0.014 \)). In comparison with screening/surveillance as an indication for colonoscopy, anaemia and rectal bleeding (\( P = 0.001 \)) were associated with significantly lower odds of satisfactory/good bowel preparation. No significance association could be observed with colitis, abdominal pain and other indications when compared with the referent group.

Univariate analyses of quality of bowel preparation as a predictor of caecal intubation rates and segmental polyp detection rates are shown in Table 3 and Figure 1. Bowel preparation quality was found to be a significant predictor of caecal intubation rates (OR 5.3, CI 3.7–7.7, \( P < 0.001 \)), although was not a significant predictor of overall polyp detection (at least one colonic polyp overall), or right- or left-sided polyp detection in patients (\( P = 0.13, P = 0.45, P = 0.54 \) respectively).

**Discussion**

In this large retrospective analysis of colonoscopies performed at a single Australian centre, a shorter preparation to procedure time was shown to be a significant predictor of adequate bowel cleansing. This finding is in keeping with recent literature showing that quality of bowel cleansing is related to the timing of administration of bowel preparation, with higher rates of adequate preparation reported with a shorter interval between completion of ingestion of bowel preparation and start of colonoscopy.14–19,23–25

---

**Table 1 Multivariate logistic regression analysis: bowel preparation to procedure (PP) interval as a predictor of quality of bowel preparation**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Satisfactory/good preparation, n (%)</th>
<th>Poor preparation, n (%)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall bowel preparation quality</td>
<td>1785</td>
<td>1557 (87)</td>
<td>228 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparation to procedure interval &gt;8 h</td>
<td>1017</td>
<td>873 (86)</td>
<td>144 (14)</td>
<td>1.3</td>
<td>0.04*</td>
</tr>
<tr>
<td>Preparation to procedure interval &lt;8 h</td>
<td>768</td>
<td>684 (89)</td>
<td>84 (11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Variables included in logistic regression analysis: preparation to procedure time, age, gender, inpatient status, indication for procedure. *Statistically significant. CI, confidence interval; OR, odds ratio (compared with preparation to procedure interval <8 h); —, no data.
Previous studies have shown that afternoon procedures are more commonly associated with poor bowel preparation. However, this finding is likely secondary to the timing of administration of the bowel preparation rather than the timing of the procedure, with a longer interval between administration of preparation to the start of the afternoon procedure leading to the poor results. Accordingly, recent studies have shown that the interval between bowel preparation and the start of colonoscopy has a significant impact on the adequacy of bowel cleansing rather than whether the procedure is performed in the morning or afternoon. Seo et al. report that a time of 3–5 h between completion of ingestion of bowel preparation and the start of colonoscopy is optimal, with an earlier study by Siddiqui et al. concluding that colonoscopy should be started within 14 h of the last dose of bowel preparation to avoid inadequate bowel cleansing, with better results achieved with a less than 8-h interval. Our study is supportive of these findings, with the shorter preparation to procedure time of <8 h for afternoon procedures leading significantly to better preparation than the longer interval of >8 h for morning procedures. As recommended by current screening guidelines, a shorter preparation to procedure time with a split preparation regimen for both morning and afternoon procedures should therefore be considered as routine. However, it is important to take into consideration patient tolerability of such a regimen, which for morning procedures remains a significant issue with patients having to get up at night to take their preparation. Transportation to the colonoscopy facility may also be an issue with patients needing to use their bowels en route. It is also prudent to consider anaesthetic risks associated with a short interval between fluid ingestion and administration of sedation.

Table 2 Multivariate logistic regression analysis: gender, age, admission status and indication for colonoscopy as predictive factors for quality of bowel preparation

<table>
<thead>
<tr>
<th>Indicator</th>
<th>n (%)</th>
<th>Satisfactory/good preparation (%)</th>
<th>Poor preparation (%)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>939 (53)</td>
<td>86</td>
<td>14</td>
<td>1.4 (1.0–1.8)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Female</td>
<td>846 (47)</td>
<td>89</td>
<td>11</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55</td>
<td>617 (34)</td>
<td>88</td>
<td>12</td>
<td>1†</td>
<td></td>
</tr>
<tr>
<td>55–69</td>
<td>564 (32)</td>
<td>87</td>
<td>13</td>
<td>1 (0.7–1.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>604 (34)</td>
<td>87</td>
<td>13</td>
<td>1.1 (0.8–1.5)</td>
<td></td>
</tr>
<tr>
<td>Admission status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>205 (11)</td>
<td>73</td>
<td>27</td>
<td>2.6 (1.8–3.7)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Outpatient</td>
<td>1580 (89)</td>
<td>89</td>
<td>11</td>
<td>0.014*</td>
<td></td>
</tr>
<tr>
<td>Indication for colonoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening and surveillance</td>
<td>608 (34)</td>
<td>92</td>
<td>8</td>
<td>1‡</td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>110 (6)</td>
<td>91</td>
<td>9</td>
<td>1 (0.5–2.1)</td>
<td>0.88</td>
</tr>
<tr>
<td>Anaemia/per rectal bleeding</td>
<td>659 (37)</td>
<td>84</td>
<td>16</td>
<td>0.5 (0.4–0.8)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Altered bowel habit</td>
<td>211 (12)</td>
<td>84</td>
<td>16</td>
<td>0.4 (0.3–0.8)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>42 (2)</td>
<td>85</td>
<td>15</td>
<td>0.5 (0.2–1.2)</td>
<td>0.13</td>
</tr>
<tr>
<td>Other</td>
<td>155 (9)</td>
<td>85</td>
<td>15</td>
<td>0.6 (0.3–1.0)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

† Odds ratios expressed comparative to age <55 as referent group. ‡ Odds ratios expressed comparative with surveillance as referent group. Multivariate analysis adjusted for covariates above (bold) in addition to preparation to procedure interval (>8 h vs <8 h). * Statistically significant. CI, confidence interval; OR, odds ratio.

Table 3 Univariate analysis: quality of bowel preparation as a predictor of caecal intubation or segmental polyp detection rates

<table>
<thead>
<tr>
<th>Indicator</th>
<th>n (%)</th>
<th>Satisfactory/good preparation (%)</th>
<th>Poor preparation (%)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caecal intubation</td>
<td>92</td>
<td>94</td>
<td>74</td>
<td>5.3 (3.7–7.7)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Overall polyp detection</td>
<td>38</td>
<td>39</td>
<td>34</td>
<td>1.2 (0.9–1.6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Left-sided polyp detection</td>
<td>28</td>
<td>28</td>
<td>26</td>
<td>1.1 (0.8–1.5)</td>
<td>0.54</td>
</tr>
<tr>
<td>Right-sided polyp detection</td>
<td>20</td>
<td>20</td>
<td>18</td>
<td>1.1 (0.8–1.6)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.
A significant finding among our cohort was the high rate of poor preparation among the inpatient group, with near to one-third of patients being poorly prepared for colonoscopy. The likely factors contributing to this high rate of poor preparation are patient immobility as well as the burden of underlying comorbid medical illness. On further review, we also noted that the majority of inpatients are planned for a morning procedure and therefore usually have a preparation to procedure interval of >8 h. Our data certainly emphasise that more attention should be paid to bowel preparation among this group, and in the light of our findings, we now tend to schedule inpatients to afternoon lists to allow additional preparation to be given on the morning of their procedure. In addition, a modified or extended regimen may be considered, and given the availability of close nursing observation, additional preparation should be given to this group when the bowel preparation is noted to be inadequate prior to the procedure. Consideration may also be given to postponing a non-urgent procedure until after a patient is discharged from hospital.

An unexpected finding among our cohort was the significant association of female gender with improved bowel preparation which is not in keeping with previous published data.10,11,27 This finding may be accounted for by variables such as compliance, which were not controlled for in the multivariate analysis conducted. Also surprising was the lack of association of age with quality of bowel preparation either as a categorical or continuous variable. This may be accounted for by the higher proportion of older patients undergoing colonoscopy for the purpose of screening or surveillance, an indication that is associated with good quality bowel cleansing. These older patients undergoing a screening or surveillance colonoscopy were also more likely to be prepared in an outpatient setting.

Our study demonstrated that adequate bowel preparation was a predictor of caecal intubation. Despite the increase in caecal intubation rates, there was not a significant increase in polyp detection (overall, or right or left sided). Multiple studies have previously demonstrated that adequate bowel preparation improves polyp detection rates.4,5,28–30 Our failure to detect improved polyp detection with better bowel preparation is likely due to a methodological flaw in our study being a failure to record the number of polyps detected overall and in each colonic segment. Thus, the reported ‘overall’ polyp detection refers to ‘at least one polyp’ detected and limits our ability to establish accurately a difference in polyp detection rates between the groups.

There are several limitations with our study. First, as a retrospective analysis, the study is subject to confounding factors, although efforts were made to adjust for these by statistical methods. Second, in our analysis of variables that may influence quality of bowel preparation, we did not control for other possible influences, such as body mass index, diverticulosis, diabetes, compliance with preparation, performance of colonoscopist, neurological conditions, pre-existing constipation and medications. The availability of anaesthetic support was also not
controlled for in the analysis; however, the number of colonoscopies performed with anaesthetic support was very small, reducing the impact of this factor on outcomes. Third, although we were able to identify those patients having split or previous day bowel preparation on the basis of the timing of their procedure, we were not able to assess for differences in type of preparation (PEG-only preparation or combination preparation) or exact timing of completion of bowel preparation. Fourth, the endoscopist reporting of bowel preparation quality as good, satisfactory or poor is subjective and does not conform to a validated scale. This represents a major flaw of the study as use of a validated bowel preparation scale significantly reduces interobserver variation in assessment of adequacy of bowel preparation. The Boston Bowel Preparation Scale is one such example where a four-point scoring system ranging from 0 (unprepared segment with mucosa not seen because of solid stool that cannot be cleared) to 3 (entire mucosa seen well with no residual staining, small fragments of stool or opaque liquid) is applied to each of the three broad regions of the colon (right colon, transverse colon and left colon).31 Last, we fail to differentiate histologically between adenomatous polyps and other colonic polypoid lesions, with ‘polyp detection’ referring to all types of polyps.

Despite the limitations of the study, it serves as a timely reminder of the importance of recognition of factors that influence adequacy of bowel preparation and therefore quality of colonoscopy (Box 1). This is important to both gastroenterologists and the wider physician audience who refer patients for the procedure, particularly with the introduction of a bowel cancer screening programme and the increasing frequency with which colonscopy is being performed. The data illustrate the significant impact of inpatient status on quality of bowel preparation, and unless there are competing urgent or mitigating factors, it may be advantageous to postpone non-urgent colonoscopy until a patient is discharged. If the procedure is to be done while an inpatient, more attention should be paid to achieving adequate preparation. Also illustrated is that the shorter the interval between completion of bowel preparation and starting the colonoscopy, the better the bowel preparation. Knowledge of procedure time (am vs pm) is therefore important when charting appropriate bowel preparation, as is liaison with anaesthetic or procedural staff as to an acceptable fasting period prior to administration of sedation. Recognition of other factors that may influence quality of bowel preparation is important, including a history of constipation, obesity, diabetes, neurological conditions and compliance with preparation. Such patients may be best prepared with a modified or extended bowel regimen, which could include a longer period with a low-residue diet, an osmotic laxative in the days leading up to the colonoscopy (epsom salts or bisocodyl), and certainly a shorter preparation to procedure time.

**Conclusion**

Our study demonstrates among a large patient cohort that a shorter preparation to procedure interval (<8 h) yields significantly better bowel preparation than a longer interval (>8 h). This illustrates the point that the timing of the administration of bowel preparation relative to the start of the colonoscopy is more important than the timing of the procedure. An awareness of factors that influence adequacy of bowel preparation is extremely important not only to gastroenterologists but the wider community who refer patients for colonscopy alike.

**Box 1. Summary box.**

- Good bowel preparation is essential for quality colonoscopy.
- A shorter interval between completion of bowel preparation and commencement of colonoscopy improves quality of bowel preparation.
- An awareness of factors which cause poor preparation is important:
  - Inpatient status.
  - Patient factors: obesity, history of constipation, diverticulosis, diabetes, neurological conditions.

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Implementation of a clinical prediction tool for pulmonary embolism diagnosis in a tertiary teaching hospital reduces the number of computed tomography pulmonary angiograms performed

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Key words
pulmonary embolism, clinical prediction tool, Wells score, computed tomography pulmonary angiography, CTPA.

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Abstract
Aim: To evaluate the effect of implementing the Wells score clinical prediction tool (CPT) on rationalising the use of computed tomography pulmonary angiography (CTPA) for diagnosing pulmonary embolism (PE).

Methods: Within a tertiary teaching hospital, a retrospective study was conducted applying Wells score to all CTPA ordered in the first quarter of 2007. Subsequently, an algorithm including Wells score and D-dimer assay was developed to assist clinicians in rationalising their ordering of CTPA. A prospective study was performed from February to August 2009 to assess the impact of this algorithm. CTPA results, D-dimer levels, referral sources and dates were recorded. The number of CTPA performed over a 7-month period following implementation of the algorithm was compared with the same period during the previous year. PE prevalence within each risk category was compared with the published literature.

Results: Three hundred and thirty-three patients were investigated with CTPA in the prospective study period. Two hundred and sixty-eight patients (80.4% of cases) had complete data. The prevalence of PE in the present study was 13.8% with 57 (21.2%) patients stratified to low risk, 169 (63.0%) to intermediate risk and 42 (15.6%) to high risk. Subgroup prevalence was 8.8%, 11.8% and 23.8% respectively. Compared with the same period in 2008, 121 (26.6%) less CTPA were performed.

Conclusion: Institutional implementation of a clinical prediction tool into the decision-making process is feasible and significantly reduces the number of CTPA being performed, with substantial cost savings and patient benefits.

Introduction
Pulmonary embolism (PE) remains a frequent and potentially fatal diagnosis that can be easily missed. As clinical assessment alone is unreliable, and the consequences of misdiagnosis are serious, a high index of suspicion and dependence on imaging techniques are required to confirm or refute a diagnosis of PE.1 As computed tomography pulmonary angiography (CTPA) has the ability to visualise directly emboli within the pulmonary arteries, good sensitivity and widespread availability 24 h per day, cases of suspected PE are often referred for CTPA soon after presentation.2 Given a positive diagnosis occurs in less than 35% of patients investigated for suspicion of PE,3 indiscriminate investigation of all such patients contributes to excessive healthcare costs and unnecessary radiation exposure. Hence, there is a need to stratify patients to ensure appropriate investigations are undertaken. While experienced clinicians rely on empirical clinical assessment (‘gestalt’) to determine the pre-test probability of PE,4 clinical scoring systems such as the Wells score1-7 have been developed and validated for use by less experienced clinicians. The aims of the present
study were twofold: (i) To review the prevalence of PE in patients investigated at a tertiary teaching hospital and estimate the pre-test probability of PE by retrospectively applying the Wells score and (ii) to implement a prospective clinical algorithm utilising the Wells score and D-dimer assay and assess whether this would improve rational use of CTPA by hospital staff. The primary outcome was whether such an algorithm could reduce the number of CTPA being performed.

Methods

Study design

A retrospective study was conducted over a 3-month period in 2007 at Box Hill Hospital in Melbourne, a tertiary teaching hospital. Patients investigated with CTPA for suspected PE were enrolled. A pre-test probability Wells score (Table 1) was enrolled to each patient based on information obtained from medical records. The criterion, ‘An alternative diagnosis is less likely than PE’ was assessed independently by three senior clinicians from different disciplines (emergency, respiratory and haematology). In cases of clinician discordance when scoring this criterion, a majority vote was used to determine the final score. All scoring physicians were blinded to the outcome of the scan. CTPA results (PE or no PE) were analysed.

The prospective study was conducted between February and August 2009. A diagnostic algorithm sheet was introduced (Fig. 1) and clinicians were encouraged to use this when assessing patients for suspected PE. Using Wells score, patients were stratified into pre-test probability categories. Those stratified high risk were investigated with CTPA. Low and medium-risk patients had D-dimer assays performed and were only imaged with CTPA if this was elevated. Completion of the algorithm form was

Table 1 Components of the simplified Wells score

<table>
<thead>
<tr>
<th>Component</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)</td>
<td>3.0</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate greater than 100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilisation (complete bedrest for 3 days in the 4 weeks before presentation) or surgery in the previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous objectively diagnosed DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy (receiving treatment, treated in the last 6 months or receiving palliative care)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

†N.B. A total score of <2 implies a low clinical pre-test probability of PE; a score of 2–6 represents a moderate clinical pre-test probability of PE; a score of >6 represents a high clinical pre-test probability of PE.2. DVT, deep vein thrombosis; PE, pulmonary embolism.

Figure 1 Suggested algorithm to substantially reduce the use of CTPA in suspected cases of PE.

CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism; USS, duplex ultrasound; V/Q, ventilation/perfusion.
required before the CT radiographers would perform a CTPA. Recorded data for each case included Wells score, date of CTPA, D-dimer level (if available) and final imaging result (PE or no PE). Additional information such as size and extent of pulmonary embolus were included for future analysis if available.

**Results**

**Retrospective study**

One hundred and fifty-four CTPA studies were performed to investigate PE – 16 studies were excluded because of missing data, and 138 studies were analysed. By calculating Wells score retrospectively, pre-test probability of PE was deemed low in 86 patients (62% of all patients), moderate in 46 patients (33%) and high in six patients (4%). Determined by CTPA, the prevalence of PE was 0% (no definite positive but one indeterminate result), 21.7% (10/46) and 50% (3/6) for the respective subgroups, with an overall prevalence of 9.7%. The overall and risk stratified subgroup prevalence of PE in the present study was similar to previously published data1,3,5 (Table 2).

**Prospective study**

Three hundred and thirty-three CTPA studies for the investigation of PE were evaluated with 65 studies excluded due to missing request forms or incomplete studies. Of the 268 studies remaining, the Wells score pre-test probabilities as assessed by the ordering clinicians were low in 57 patients (21%), moderate in 169 patients (63%) and high in 42 patients (16%). The CTPA prevalence of PE was 8.8% (5/57), 11.8% (20/169) and 23.8% (10/32) for the respective subgroups. The overall prevalence of PE in 2009 was 13.8%, similar to 13.6% over the same period in 2008 (Table 3).

Compared with the same period (February to August) in 2008 (454 CTPA), 26.6% (121) less CTPA were performed in 2009 (333). There were reductions in requests from the emergency department (12%), inpatients (45%), intensive care unit (ICU) (27%) and outpatients (60%) (Tables 4 and 5).

**Discussion**

The present study supports the utility of a validated clinical prediction tool in guiding clinical practice in a tertiary teaching hospital setting. Our retrospective study confirmed the robust nature of the Wells score with risk stratified PE prevalence comparable to those previously reported.1,6,7,9,10 The prospective study demonstrated that using a diagnostic algorithm combining Wells score, D-dimer results and rational ordering of CTPA, PE can be diagnosed or ruled out safely and is associated with a

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**Table 2** Overall and risk stratified subgroup prevalence of pulmonary embolism in previous studies compared with the present study

<table>
<thead>
<tr>
<th>Study</th>
<th>Wells et al. 2007</th>
<th>Chagnon et al. 2002</th>
<th>Yap et al. 2007</th>
<th>Box Hill Hospital study 2007</th>
<th>Box Hill Hospital study 2009 (current study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 1219 (62%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low probability</td>
<td>3% (40)</td>
<td>12% (58)</td>
<td>4% (66)</td>
<td>0% (63)</td>
<td>8% (21)</td>
</tr>
<tr>
<td>Intermediate probability</td>
<td>20% (52)</td>
<td>40% (38)</td>
<td>13% (31)</td>
<td>22% (33)</td>
<td>11% (63)</td>
</tr>
<tr>
<td>High probability</td>
<td>63% (41)</td>
<td>91% (4)</td>
<td>67% (3)</td>
<td>50% (4)</td>
<td>23% (16)</td>
</tr>
<tr>
<td>Overall prevalence</td>
<td>16%</td>
<td>26%</td>
<td>9%</td>
<td>9%</td>
<td>14%</td>
</tr>
</tbody>
</table>

†Unpublished data – results presented at Thoracic Society of Australia & New Zealand Annual Scientific Meeting (Victoria) 2008. The numbers in parentheses represent the % of all Wells scores from each study that fell into the respective probability group.

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**Table 3** Prevalence of pulmonary embolism (PE)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients screened for PE (a)</th>
<th>Positive result of PE on CTPA (b)</th>
<th>Negative result of PE on CTPA</th>
<th>Prevalence ((a/b)*100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>454</td>
<td>62</td>
<td>392</td>
<td>13.6%</td>
</tr>
<tr>
<td>2009</td>
<td>333</td>
<td>46</td>
<td>287</td>
<td>13.8%</td>
</tr>
</tbody>
</table>

CTPA, computed tomography pulmonary angiography.

**Table 4** Source of computed tomography pulmonary angiography requests

<table>
<thead>
<tr>
<th>Emergency department</th>
<th>Inpatients</th>
<th>ICU</th>
<th>Outpatients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>244 [53%]</td>
<td>194 [42%]</td>
<td>11 [25%]</td>
</tr>
<tr>
<td>2009</td>
<td>215 [64%]</td>
<td>107 [32%]</td>
<td>8 [25%]</td>
</tr>
<tr>
<td>Difference</td>
<td>−29 [12%]</td>
<td>−87 [45%]</td>
<td>−3 [27%]</td>
</tr>
</tbody>
</table>

ICU, intensive care unit.
significant reduction in the number of CTPA performed over a comparable historical time period. Furthermore, this can be generally applied to junior medical staff with a broad range of clinical experience in a teaching hospital setting. There is evidence in the literature that demonstrates similar accuracies between pre-test probabilities assigned through clinical gestalt (senior clinician) and prediction rules (junior medical staff) especially in the low and high-risk groups.

The reduction in CTPA use has health and economic benefits. First and foremost, CTPA has serious established side effects including contrast-related renal impairment and a non-negligible increase in malignancy particularly in breast tissue. Younger patients are at greatest risk. It is estimated that a 20-year-old woman receiving a CTPA or coronary artery/abdominal-pelvis imaging may have an associated increase in the risk of malignancy of up to 1 in 80. Radiation doses in clinical practice have also been found to be higher than commonly reported, varying substantially within and between facilities due to non-standardised imaging protocols resulting in additional scan length or passes. The frequent use of CTPA also results in incidental nonvascular findings of uncertain significance. This may subject patients to additional invasive/irradiating diagnostic procedures, contributing further to patient risk and healthcare costs while ‘true positive’ results of significance in these incidental findings are typically very low.

The cost savings from performing fewer CTPA in the present study were substantial. Based on the Medicare (Australian National Health Service) item number cost (Medical Benefits Schedule Number 57350) alone, AUD$61 710 was saved by performing 121 fewer CTPA assuming a cost of AUD$510 per investigation. This does not take into account the cost of consumables (contrast, IV lines), CT technician and reporting radiologist time costs which would increase this figure further. These savings are crucial considering that advanced imaging methods are the fastest-growing physician-directed expenditures.

In our prospective study, the number of patients in the pre-test probability groups, particularly the low numbers in low risk and large numbers in intermediate risk, was dissimilar to previous studies. The reduced numbers stratified to low risk seen in the prospective study were most likely due to patients initially considered for PE, but evaluated to be of low risk under the algorithm and subsequently discharged without imaging. These patients were not followed up due to logistical reasons given previous evidence that this was a safe clinical strategy. The greater than expected number of patients stratified to intermediate risk may have been due to unique characteristics in the population of our health service catchment area (elderly patients with multiple comorbidities, tertiary teaching hospital), which may have introduced some selection bias. Inconsistencies in risk stratification by junior clinical staff could also have introduced bias, especially when it came to the subjective component of the Wells score (‘alternative diagnosis is less likely than PE’). The predictive value of the Wells score has previously been shown to be derived primarily from its subjective component. It is also conceivable that junior doctors may have given an inappropriately high Wells score, even if clinically inaccurate, in order to obtain a CTPA to rule out PE. There is great temptation to request investigations that exclude other pathologies simultaneously even if clinical circumstance may not warrant so. Accountability over failure to diagnose serious abnormalities is significant, whereas liability arising from the overuse of testing is exceedingly rare.

We acknowledge several limitations to the present study. The exclusion of 65 (19.5%) patients from our cohort of patients who underwent a CTPA due to an incomplete or absent Wells score triage form was not ideal. It is reflective of the challenges that face any well intentioned move to change institutional practices. We concede that the introduction of the clinical prediction tool only partially fulfilled the expected outcome of an increase in the number of positive studies with a smaller number of total studies performed. The latter objective was achieved, but this was associated with prevalence rates that were similar in the two successive years compared. It is possible that the true prevalence of patients with PE was much higher as they were more appropriately selected with the algorithm, but the patients were diagnosed with ventilation/perfusion (V/Q) scanning rather than CTPA. The lack of barriers to requesting a V/Q scan may have inadvertently shunted patients to this test.

We used 2008 as our reference year as it was the most recent and convenient. Within the present study limitations, we did our best to sample a representative
number of months and their corresponding periods the year before in order to improve parity when comparing data. We were not aware of any exceptional factors that would dramatically influence the prevalence of patients with PE presenting to hospital but do recognise that variations can occur throughout the year including factors beyond our control that may for example, artificially inflate figures in 2008, thus reducing the effect size from our prediction tool on PE prevalence. If resources and time permitted, retrospective analysis of the last few years leading up to the study period would have been ideal.

Another factor for consideration in the present study and generally, is the dichotomous classification of CTPA result as being ‘positive’ or ‘negative’ for PE. The improved visualisation of segmental and sub-segmental arteries with multi-detector CT has raised concerns about over-diagnosis of peripheral PE.\textsuperscript{21,22} The clinical relevance of small peripheral pulmonary emboli and the need to administer anticoagulants in such cases remains a subject of debate. While beyond the scope of this paper, there appear to be subsets of patients with a small PE, and no deep venous thrombosis in whom the risks associated with anticoagulation outweigh the benefits.\textsuperscript{23}

**Conclusion**

We have demonstrated that a validated clinical prediction tool and diagnostic algorithm can be broadly used in a tertiary hospital setting with potential savings in healthcare resources and reduction in patient risks by averting unnecessary presumptive treatment and diagnostic testing. Implementation of such well-meaning interventions requires long-term persistence and consistency to ensure uptake and appropriate application of the clinical prediction tool.

**References**

Queensland Lung Cancer Screening Study: rationale, design and methods


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Key words
lung neoplasms/radiography, radiography, thoracic, tomography, X-ray computed/*adverse effect, tomography, X-ray computed/*method, mass screening.

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Abstract
Background: Lung cancer is the leading cause of cancer-related mortality in Australia. Screening using low-dose computed tomography (LDCT) can reduce lung cancer mortality. The feasibility of screening in Australia is unknown. This paper describes the rationale, design and methods of the Queensland Lung Cancer Screening Study.
Aims: The aim of the study is to describe the methodology for a feasibility study of lung cancer screening by LDCT in Australia.
Methods: The Queensland Lung Cancer Screening Study is an ongoing, prospective observational study of screening by LDCT at a single tertiary institution. Healthy volunteers at high risk of lung cancer (age 60–74 years; smoking history ≥30 pack years, current or quit within 15 years; forced expiratory volume in 1s ≥50% predicted) are recruited from the general public through newspaper advertisement and press release. Participants receive a LDCT scan of the chest at baseline, year 1 and year 2 using a multidetector helical computed tomography scanner and are followed up for a total of 5 years. Feasibility of screening will be assessed by cancer detection rates, lung nodule prevalence, optimal management strategies for lung nodules, economic costs, healthcare utilisation and participant quality of life.
Conclusions: Studying LDCT screening in the Australian setting will help us understand how differences in populations, background diseases and healthcare structures modulate screening effectiveness. This information, together with results from overseas randomised studies, will inform and facilitate local policymaking.

Introduction

Disease burden
Lung cancer is the fifth most common cause of cancer in Australia but the leading cause of cancer-related mortality. In 2001, $A136 million were spent on the condition.1 Five-year survival remains poor (12% in 1998–2004) and has changed little in recent decades.2 Although smoking...
rates are decreasing, cancer incidence lags 20 years behind smoking trends, and so coupled with an ageing population, new cases increased from 6310 in 1985 to 9563 in 2006 and are predicted to rise further as the population grows and ages. Over 50% of newly diagnosed lung cancer patients are former, not current, smokers, and former smokers now outnumber current smokers. In 2007, 16.6% of Australians smoked daily, whereas 25.1% were ex-smokers. The combination of poor outlook, lag time and a large population ‘at risk’ means that lung cancer will remain a significant burden of disease over coming decades.

**Screening with computed tomography**

**Observational studies**

As the population at risk is relatively well defined and early stage disease is potentially curable, lung cancer outcomes could be improved by screening. Screening with chest radiographs (CXR) failed to show benefit and this has been confirmed by the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Observational studies using low-dose computed tomography (LDCT) showed this modality was three to four times more sensitive in detecting tumours than CXR. Upwards of 70% of non-small cell lung cancers detected at baseline were stage I compared with 20% expected in clinical practice. Baseline cancer prevalence ranged between 0.2% and 2.7%, being lower in studies which enrolled never smokers and/or younger participants.

**Randomised, controlled studies**

Following the encouraging results from observational studies, two large randomised, controlled trials (RCTs) powered to detect statistically significant lung cancer mortality differences were initiated: the National Lung Screening Trial (NLST) in the United States and the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) Trial in Holland/Belgium. The NLST, a collaboration of the Lung Screening Study and American College of Radiology Imaging Network (NLST-ACRIN) funded by the US National Cancer Institute, randomised 53,454 volunteers to screening by LDCT or CXR, and recently reported a 20% mortality benefit. The NELSON study randomised 15,428 participants to LDCT screening or usual care (no screening), and is expected to reach its primary endpoint in 2015.

**The Queensland Lung Cancer Screening Study: design and aims**

The Queensland Lung Cancer Screening Study (QLCSS) is an observational cohort study setup to determine LDCT screening feasibility in Australia. During planning, it was unclear whether LDCT screening would reduce lung cancer mortality. The design was based on the NLST LDCT-arm protocol, with the aim that this would enable QLCSS to inform a future health technology and economic assessment of LDCT implementation in Australia should NLST show benefit.

The expected baseline cancer prevalence is 1–2%. We initially planned to recruit 750 volunteers to assess lung nodule prevalence, cancer prevalence/incidence, nodule management strategies, economic costs, healthcare utilisation and participant quality of life. We will also identify screening-associated smoking cessation opportunities and assess feasibility of biomarker collection. This paper describes the QLCSS methods with particular reference to local adaptation from the NLST protocol.

**Methods**

**Ethical considerations**

Volunteers give informed consent; the study has approval from the Hospital and University Medical Research Ethics Committees and is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12610000007033). Medical physicists developed the low-dose radiation protocol according to national guidelines. An external Data and Safety Monitoring Board monitors the study. NLST-ACRIN gave permission to use and adapt their protocol.

**Participants**

Screening effectiveness depends in large part on disease prevalence. Prevalence determines detection rate independently of test sensitivity or specificity; thus, choosing a high-risk population is fundamental.

The most important lung cancer risks are smoking, accounting for 84% and 77% of cases in Australian men and women, respectively, and age. Cancer incidence increases from 61 per 100,000 persons (age-standardised incidence, ASI) in the 50- to 59-year age group to 107, 180 and 243 in the 60–64, 65–69 and 70–74 year age groups respectively.

Potential screening benefits have to be balanced against potential risks, including radiation-induced cancer. For most organs, cancer risk decreases with increasing age at time of exposure. However, lung cancer risk peaks around 50–55 years of age and interacts synergistically with smoking. Thus, the population targeted by screening is also most susceptible to radiation-induced lung cancer. Therefore, QLCSS uses the NLST eligibility criterion of ≥30 pack years of smoking (ex-smokers must...
have quit within the previous 15 years) but has increased the age limits from 55–74 years (NLST) to 60–74 years (see ‘Radiation Risk’ later).

Inclusion and exclusion criteria

Table 1 details QLCSS entry criteria. We exclude volunteers unable to give informed consent, those with significant comorbidity and those in whom scan quality is anticipated to be poor. Lung function per se is not part of NLST criteria, but in QLCSS, a threshold of forced expiratory volume in 1 s (FEV1) < 50% predicted excludes participation to ensure that screenees have a reasonable chance of tolerating curative surgery.

LDCT protocol

We use a 64-detector helical computed tomography (CT) scanner (Philips Brilliance, Philips Medical Systems, Best, the Netherlands), with the following scout scan parameters: 120 kV, 30 mA, 350 mm scan length, 3.7-s scan time. NLST uses 96 different scanners ranging from 4- to 64-detector rows with varied scan parameters. A comparison of QLCSS and NLST parameters (two 64-detector scanners and overall ranges) is presented in Table 2. To minimise breathing artefact, participants are instructed to take a full breath in and full breath out twice, holding the third full breath for the scan duration.

Radiation risk

Radiation-induced lung cancer risk estimates have been derived using data from atomic bomb survivors and appear higher for younger, smoking females and lower for older, ex-smoker males. Using CT Expo V1.5.1 (Medizinische Hochschule, Hannover, Germany; available at URL: http://www.mh-hannover.de/1604.html?6l=1), we estimated an Effective Dose from one scan using our LDCT protocol (including scout view) of 0.84 mSv for (70 kg) males and 0.94 mSv for (60 kg) females. Effective dose reflects the overall potential biological detriment from an exposure and is a sex-averaged dose calculation using various assumptions such as the radiation sensitivity of different organs, and imaging technique and protocols. Our estimates fall within the Australian Radiation Protection and Nuclear Safety Agency guidelines for research participants (total Effective Dose for adults over 60 years old should not exceed 8 mSv in any year or 10 mSv across 5 years) and compare with 0.02 mSv from a single posterior-anterior CXR, 7 mSv from a conventional CT chest and 1.5 mSv/year from background radiation. Using Brenner’s methods, the estimated excess fatal radiation-induced lung cancers in

Table 1 Queensland Lung Cancer Screening Study inclusion/exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age 60–74 years and 364 days</td>
</tr>
<tr>
<td>• Current or previous cumulative cigarette smoking history of &gt;30 pack years (packs per day multiplied by the number of years smoked)</td>
</tr>
<tr>
<td>• Former smokers must have quit smoking within the previous 15 years</td>
</tr>
<tr>
<td>• With or without asbestos exposure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Medical comorbidity and poor lung function</td>
</tr>
<tr>
<td>• Individuals unlikely to complete curative lung cancer surgery (e.g. thoracotomy with lobectomy or pneumonectomy – i.e. poor lung function, FEV1 &lt; 50% predicted, with no bronchodilator use within previous 12 hours)</td>
</tr>
<tr>
<td>• Domiciliary oxygen for respiratory conditions</td>
</tr>
<tr>
<td>• Any medical condition that poses a significant risk of mortality during the trial period</td>
</tr>
<tr>
<td>• Any medical or psychiatric condition precluding informed consent</td>
</tr>
</tbody>
</table>

CT, computed tomography; FEV1, forced expiratory volume in 1 s.
our population range from 50 per 100,000 screenees for female current smokers aged 60 to 1 per 100,000 screenees for older male former smokers (Table 3).

Recruitment

QLCSS recruits general public volunteers through newspaper advertisements and press releases that summarise eligibility criteria and the study outline. Indigenous groups are not specifically targeted. NLST used various strategies such as targeted mailings, newspaper advertisements and web sites. Potential participants contact the research office and are sent an information pack and demographics/medical questionnaire. Volunteers meeting preliminary criteria are sent further information and consent forms for screening, blood and remnant tissue collection (for biomarker analysis), and questionnaires regarding quality of life, health status, smoking history, occupational and asbestos exposure. Smokers are provided with written cessation materials. Volunteers considered eligible attend for spirometry and, if FEV1/H1350 < 50% predicted, proceed to their baseline LDCT scan.

Timeline

Figure 1 illustrates participant flow through QLCSS. As with NLST, volunteers are screened at enrolment (prevalence scan) and have two further scans at 12-month intervals (incidence scans). Some flexibility is allowed in scheduling incidence scans – up to 1 month prior and 3 months after the due date. To minimise the potential confounder of inflammatory nodules, scans are post-

Table 2 Comparison of scanner parameters in QLCSS and NLST

<table>
<thead>
<tr>
<th>Parameter</th>
<th>QLCSS</th>
<th>NLST&lt;sup&gt;14,15&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanner</td>
<td>Phillips Brilliance 64</td>
<td>Siemens Sensation 64</td>
</tr>
<tr>
<td>kV</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Gantry rotation time [s]</td>
<td>0.75</td>
<td>0.5</td>
</tr>
<tr>
<td>mAs (regular patient–large patient values)</td>
<td>25–70</td>
<td>50–100</td>
</tr>
<tr>
<td>mAs (Reg–Lg)</td>
<td>25–50</td>
<td>25–50</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>50–70</td>
<td>25</td>
</tr>
<tr>
<td>70–80</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>80–100</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>100–150</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>150–180</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>180–200</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Scanner effective mAs‡ (Reg–Lg)</td>
<td>25–70</td>
<td>25–50</td>
</tr>
<tr>
<td>Detector collimation (mm) – T</td>
<td>0.625</td>
<td>0.6</td>
</tr>
<tr>
<td>Number of active channels – N</td>
<td>64</td>
<td>32</td>
</tr>
<tr>
<td>Detector configuration – N × T</td>
<td>64 × 0.625</td>
<td>32 × 0.6</td>
</tr>
<tr>
<td>Collimation (on operator console) (mm)</td>
<td>0.9</td>
<td>64 × 0.6</td>
</tr>
<tr>
<td>Table incrementation (mm/rotation) – I</td>
<td>30</td>
<td>19.2</td>
</tr>
<tr>
<td>Pitch ([mm/rotation]/beam collimation) – I/NT</td>
<td>0.92</td>
<td>1.0</td>
</tr>
<tr>
<td>Table speed (mm/s)</td>
<td>49.2</td>
<td>38.4</td>
</tr>
<tr>
<td>Scan time (40 cm thorax) [s]</td>
<td>9.57</td>
<td>11</td>
</tr>
<tr>
<td>Nominal reconstructed slice width [mm]</td>
<td>0.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Reconstruction interval [mm]</td>
<td>0.45</td>
<td>1.8</td>
</tr>
<tr>
<td>Reconstruction algorithm§</td>
<td>8</td>
<td>830</td>
</tr>
<tr>
<td>Images/data set (40 cm thorax)</td>
<td>888</td>
<td>223</td>
</tr>
<tr>
<td>CTDIvol mGy¶</td>
<td>1.5–4.1</td>
<td>1.9–3.8</td>
</tr>
</tbody>
</table>

Adapted from Cagnon et al.<sup>14</sup> †The lower exposure bound is a guideline; lower exposures are acceptable provided that diagnostic image quality is preserved. The upper exposure is a fixed limit. ‡For Siemens and Philips scanners, users input ‘effective mAs’ or ‘mAs slice’ at the scanner console, which is defined as (mA × time)/pitch. For others, this value is calculated for comparison only. §Reconstruction parameters required by the NLST-ACRIN protocol; sites may create additional reconstructions with other intervals and algorithms. ¶CTDIvol represents dose measured in 32 cm acrylic phantom, not radiation dose to a patient. NLST sites may see variations up to ±20%. CTDI, computed tomography dose index; I, increment – the table increment per rotation of the X-ray tube in a helical scan; N, number of data channels or the actual number of data channels used during an acquisition; NLST, National Lung Screening Trial; NLST-ACRIN, NLST–American College of Radiology Imaging Network; QLCSS, Queensland Lung Cancer Screening Study; T, Z axis collimation (width of one data channel) – several detector elements may be grouped together to form one data channel; —, no data.
pended by 6 weeks if intercurrent respiratory tract infection is reported or by 3 months if antibiotics have been prescribed. Screenees’ health status is checked by mailed questionnaires for a total of 5 years.

Scan interpretation

Scans are viewed on workstations and independently read by two thoracic radiologists. As interreader variability is recognised to be high, even among experienced radiologists, scans are reviewed at a consensus meeting of radiologists and thoracic physicians to resolve differences and annotate findings. If available, historical CT images are obtained for comparison at the consensus meeting. Incidence scans are read blind but compared with baseline and interval scans at the consensus meeting for interval change.

The radiologists read 0.9 mm thin-slice or 5 mm maximum intensity projection reconstructions but record all measurements from thin slices using computerised callipers. Nodules are categorised by maximal axial dimension as micronodules (<4 mm diameter) or nodules (≥4 but <30 mm), as per the NLST protocol. For nodules ≥4 mm, a perpendicular axial measurement is also recorded, along with density (soft-tissue, groundglass, mixed/part-solid), margin characteristics (smooth, speculated, ill-defined) and location (lobe, pleural proximity; Fig. 2).

Nodules with benign calcification patterns are classified as granulomas. We initially recorded fissural and pleurally attached micronodules but abandoned this when others documented a very low probability of malignancy. A positive screening scan is defined as one or more non-calcified nodules ≥4 mm diameter or other lesion(s) suspicious for cancer. Each scan is given an overall subjective rating for suspicion of cancer (none/low/intermediate/moderate/high).

Computer-aided detection (CAD) and semiautomated volumetric software (Philips Brilliance v2.6.0.32) are used to evaluate the utility of CAD as a ‘second reader’ and to measure the volume of nodules ≥4 mm. The software automatically searches for candidate nodules that can be accepted or rejected by the reader. Automatic segmentation can be manually adjusted slice by slice if required, e.g. for juxtapleural or juxtavascular nodules.

Incidental non-nodule findings are reported to the general practitioner and participant with a recommendation for follow up if necessary.

Nodule management

Nodule size at baseline scan correlates with lung cancer risk. Thus, nodule size largely dictates management in accordance with NLST (Fig. 3). Micronodules are followed up at 12 months, as the risk of malignancy is considered very low. Participants with nodules ≥4 mm are assessed clinically and usually followed up with interval scans (low-dose protocol limited to nodule whenever possible). Nodules <10 mm diameter are generally too small for biopsy, but larger nodules (≥10 mm) are amenable to attempted tissue diagnosis. Nodules that remain stable over 2 years of follow up are considered benign.

All participants with a positive scan (i.e. one or more nodules ≥4 mm diameter) are recommended to have clinical review by a thoracic physician. QLCSS does not mandate investigation and management outside of the recommendations in Figure 3.

Nodule growth is an important finding. Any growing nodule approaching 10 mm diameter or greater is considered for CT-guided or bronchoscopic biopsy depending on its location. Empirical antibiotics have been suggested as a first step in management; however, there is evidence against this approach, and we do not use antibiotics in the absence of symptoms. Surgical intervention without positive proof of malignancy is not ideal and avoided, if possible.

Participants diagnosed with cancer are offered standard treatment through a multidisciplinary team of physicians, radiologists, oncologists, surgeons and palliative care.

Economic data

Knowledge of the costs of screening is fundamentally important. We use patient diaries, Medicare data and hospital episodes to gather data on all medical and

| Table 3 Estimated number of excess lung cancer deaths per 100 000 screenes associated with the low-dose computed tomography procedure protocol in the Queensland Lung Cancer Screening Study |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age at time of first scan (years) | Male | Female | Male | Female |
| Current | Former | Current | Former |
| smoking status | smoking status | smoking status | smoking status |
| Single computed tomography scan | 60 | 4.9 | 3.5 | 18.7 | 13.7 |
| 65 | 3.1 | 2.3 | 12.1 | 9.1 |
| 70 | 1.6 | 1.3 | 5.6 | 4.7 |
| 75 | 0.6 | 0.6 | 1.6 | 1.9 |
| Three successive scans at 1-year intervals | 60 | 13.7 | 9.7 | 52.2 | 38.2 |
| 65 | 8.5 | 6.3 | 32.4 | 24.7 |
| 70 | 4.1 | 3.4 | 14.3 | 12.4 |
| 75 | 1.8 | 1.9 | 4.8 | 5.6 |

Rates are for current and former smokers exposed to estimated lung doses of 2.3 mGy per scan.
health-system resource costs regardless of relationship to lung cancer. Standard costing methods (Department of Health and Ageing) are used, that is, Pharmaceutical Benefits Advisory Committee, Medicare Benefits Scheme, Australian-Refined Diagnosis-Related Groups codes, Australian National Sub-Acute and Non-Acute Patient Classification System codes, and National Hospital Data Collection costing for outpatient and ambulatory care. This information will be used to feed into the economic model proposed by Manser for the Australian health setting.22

Discussion

We based QLCSV on the NLST protocol because NLST was expected to be the first RCT to reach its primary endpoint. Indeed, in 2011, NLST reported a 20% lower lung cancer-specific mortality rate in the LDCT-screened arm compared with the CXR-screened arm, demonstrating for the first time that screening can reduce lung cancer mortality. Although a landmark study, questions regarding feasibility and cost still remain, and careful exploration of screening in the Australian context is therefore required.

Screening is a complex process, the subtleties of which are often not fully appreciated by the public and practitioners alike, as exemplified by the current debate surrounding mammographic breast screening. This may seem somewhat surprising given the apparently well-established place of breast screening in many countries, including Australia since 1991. Questions regarding risk-benefit, overdiagnosis and, ultimately, effectiveness of...
breast screening have led to several countries re-evaluating their programmes; for example, the US and Canadian Preventive Services Task Forces both now recommend restricting screening to women between the ages of 50 and 74 years (every 2–3 years), and in the UK, an independent evaluation of the breast screening program is underway. This debate underscores the complexity of screening and the need for contemporary data to inform a service that can, and should, evolve.

An effective screening programme relies not only on an effective test, but also on an effective system to deliver the service and follow up results. Perhaps uniquely in the world, Japan has enthusiastically adopted mass screening for lung cancer using CXR. Notwithstanding the now overwhelming weight of evidence against CXR screening, it appears that the lack of a central quality control framework compounded problems of low detection rates and wide variations in compliance and follow up. This highlights the requirement of robust systems to assure adequate programme delivery.

Populations, background disease, healthcare structures and resources vary between countries and mean that screening programmes are specific to their intended population. The International Association for the Study of Lung Cancer states, ‘an assessment of lung cancer screening benefit, implementation costs and potential harms must be defined in a cultural context, so that national policies about screening implementation and issues such as quality control and professional credentialing standards can be decided.’ Thus, a trial in Australia is necessary and will be able to provide useful data for this country.

Differences between the USA and Australia that may impact on screening include benign granulomatous conditions such as histoplasmosis, endemic in parts of the USA, which could increase the risk of false-positive results. Exposure to non-tobacco lung cancer risk factors may also vary; for example, many Australians have been exposed to asbestos that was used extensively in domestic buildings. Lung cancer incidence is lower in Australia: in 2008, the USA ASI per 100 000 was 49 (men) and 36 (women) compared with 33 (men) and 19 (women) in Australia. The outcome of differences in cancer incidence and false-positive rates is difficult to predict but could affect screening efficiency, adverse event rates and cost-effectiveness.

The ideal recruitment strategy for lung cancer screening has yet to be determined. As expected, screening studies are subject to healthy volunteer bias. Although this should not impact on the relative outcomes between intervention and control groups in RCTs, participants of lower socioeconomic status (SES) tend to be underrepresented. As lower SES is associated with both higher incidence and worse outcomes in lung cancer, ways of targeting these groups in the ‘real world’ setting must be considered. The QLCSS, as an observational study, may thus overestimate or underestimate effectiveness of screening when applied to the real-world situation; participants may have lower rates of cancer but higher screening compliance and higher rates of smoking cessation.
Another consideration for Australia is access to screening, particularly for isolated communities. Relocatable screening services and mobile screening vans are used for breast screening,12 and although mobile CT scanners have been used for lung cancer screening in Japan,33 as far as we are aware, this has never been tested in remote areas.

Scan reading and nodule measurement methods are also yet to be optimised. Double-reading detects more nodules than single-reading34 but is time-consuming. QLCSS scans are double-read; NLST uses single readers. Because QLCSS is a small study, double-reading is feasible. This will not be practicable for large-scale screening; however, CAD may have utility as an inexpensive ‘second reader’. Nodule measurement methods are also debated. Linear measurement is very convenient but subject to high interreader and intrareader variability.35 Volumetric measurement may be more accurate in detecting interval growth36 and is the primary method in NELSON. QLCSS collects both measurements and will be able to make a direct comparison between 2D and volumetric measurement.

Although LDCT scans are subject to increased noise and show poorer resolution of mediastinal structures than conventionally dosed scans, this is not an issue when assessing lung nodules because of the high contrast between low-attenuation lung and higher attenuation nodules. Several studies have confirmed LDCT’s adequacy for screening.37–40 LDCT is the current standard for screening, but the dose may even be able to be reduced further (‘ultra low dose’) using smoother reconstruction filters to reduce image noise.41 The most important question that remains unanswered is the financial cost of screening. This is not only accrued through delivery of screening and detection of cancer but also by ‘negative’ aspects of screening, such as overdiagnosis and false-positive rates. These unwanted outcomes adversely affect participant quality of life and increase costs by decreasing screening efficiency through unnecessary follow up and diagnosis. NLST will publish cost-effectiveness data soon. Given the differences in health structures and funding between the USA and Australia, compilation of direct and indirect cost data from QLCSS will allow rational health economic modelling relevant to Australia to be undertaken.

Conclusions

QLCSS, based on the NLST protocol but recruiting a slightly older cohort, commenced recruitment in 2007 to allow extrapolation of NLST results to the Australian setting and understand the influence of different populations, risk factors and competing disease. Given the differences between populations and healthcare structures, and with several other screening issues still in discussion, it is desirable to gather local data prior to consideration of any national programme, even in the face of positive results from NLST. This Australian study will enable overseas results to be interpreted in context and build capacity in this complex and evolving area.

Acknowledgement

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Radiation Protection Series No. 8; 2005.


26 Richards M. An independent review is under way. BMJ 2011; 343: d6843.


Unmet needs of people with end-stage chronic obstructive pulmonary disease: recommendations for change in Australia

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Key words
chronic obstructive pulmonary disease (COPD), model of care, palliative approach, end-of-life care, health policy.

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is an increasing cause of mortality. However, people with COPD are unlikely to receive care that meets the needs of themselves or their carers at the end of life.

Aims: To explore the needs of people with end-stage COPD in South Australia and develop recommendations for a model of care.

Methods: Three related studies were undertaken: in Study 1, 15 people with advanced COPD and their carers were interviewed twice, 6 months apart; Study 2 investigated views of an Expert Panel and Study 3 conducted focus groups and interviews with service providers and community groups to examine service availability and accessibility.

Results: This project demonstrated that the needs of people with COPD are not being met. There was an absence of a coordinated pathway for support. Care was fragmented, episodic and reactive. The role of carers was poorly recognised. Health professionals identified the lack of a clear transition to an end-stage and significant barriers to obtaining support for activities of daily living. Communication issues were identified in all studies, including the absence of advance care planning conversations.

Conclusions: A flexible model of care is needed that assists people with COPD to navigate the health system. This should be patient centred and coordinated across primary, acute and community sectors. Neither respiratory nor palliative care services alone can adequately support people with COPD. The integration of a multidisciplinary palliative approach within a chronic disease management strategy will be central for the best care for people living with advanced COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major and increasing cause of mortality both in Australia and internationally1,2 with COPD and allied diseases associated with 3.7% of all deaths in Australia in 2005.3 In 2008, the estimated financial cost of COPD in Australia was $8.8 billion, with care both in hospital and in the community becoming an increasing burden. It was also estimated that a further $89 billion was lost due to disability and premature death.3

The needs of people with COPD and their carers are becoming more clearly documented,4,5 and patients dying of chronic lung disease may experience physical symptoms and psychosocial distress at least as severe as patients with lung cancer.6 Nevertheless, they are less likely to gain adequate symptom control or receive care that meets the needs of themselves or their carers at the end of life.5,6

Current models of palliative care have developed almost exclusively around the needs of people with cancer,7 with no consensus in the literature about which aspects of palliative care best meet the needs of non-cancer patients.7 It is increasingly being recognised that a palliative approach should be an integral part of healthcare provision and available to all who need it.8 The Australian COPD-X guidelines highlight that ‘Unlike the cancer trajectory, the intermittent and potentially reversible acute exacerbations of COPD make palliative referral and discussion about end of life care difficult to initiate.’9 The guidelines point to clinical indicators of shortened survival and in the presence of functional deterioration, a staged approach to adjusting the goals of care.9 While they recognise the role of specialist palliative care services...
and the importance of incorporating a palliative approach, to date, there is no Australian model of COPD care which incorporates this and specifically addresses the needs of people with end-stage COPD.

Method

A qualitative multi-perspective approach was chosen to ensure that any model of care was informed by the voices of people with COPD and their carers and key service providers, including professionals from respiratory health, palliative care, primary care and community-based services in order to develop practical recommendations. Three separate related studies were undertaken:

Study 1: people living with COPD and their carers: exploring their needs

Selection

People with advanced COPD and their carers were recruited through a major urban hospital and its rural outreach clinic. Rigorous selection criteria informed by a literature review and expert opinion were developed. A purposive sample was recruited by the respiratory nurse specialist who reviewed case notes and approached eligible patients. Participants with COPD were over 18 years of age, fluent in English, had been hospitalised at least twice in the past 12 months with a respiratory illness, satisfied Global Initiative for Chronic Obstructive Lung Disease Stage IV classification for COPD severity, were sufficiently robust to tolerate an interview and were free from obvious cognitive impairment. Exclusion criteria included active treatment for lung cancer in the past 5 years or any metastatic cancer, lung transplantation or living in residential care.

Data collection

Issues associated with the participants’ care needs and their experiences of living in the community with severe COPD were explored by an experienced qualitative researcher in two in-depth interviews 6 months apart. Carers were offered a separate interview but generally joined with their partner. Data were collected about performance status, the degree of dyspnoea and impact of the illness on quality of life. Participants’ and carers’ knowledge of advance directives and experience of advance care planning was also discussed. All interviews were recorded, transcribed and combined with field notes.

Study 2: issues and challenges associated with advanced COPD: the views of specialist health professionals

Selection

The aim of Study 2 was to establish an Expert Panel of respiratory, palliative medicine, general medical practitioners (GP) and specialist respiratory and palliative care nurses.

Data collection

The Expert Panel met twice to refine COPD morbidity and mortality data in order to identify a transition to the end-of-life period for use in policy planning and service development. Questions in Panel 1 focused on identifying the transition to end-of-life care and referrals to palliative care, while Panel 2 focused on the needs of the person with COPD as the end of life approached and how these might be assessed; the organisational changes needed for managing advanced disease; what assessment tools might be used and by whom and when symptom control should become the focus of care. Both Expert Panel discussions were audio-recorded, and notes were taken of key issues arising throughout the discussions.

Study 3: service availability and accessibility for people with advanced COPD and their carers

Selection

It was agreed that key service providers in the areas of respiratory and palliative care could provide detailed insights into the accessibility and availability of services for people with advanced COPD. A purposive sampling technique was used to identify participants from a variety of professions and disciplines across the community, primary care and acute care systems, and information was supplemented by input from a community-based consumer support group and from Carers SA.

Data collection

A series of discipline-specific focus groups, interviews and group meetings was undertaken. An interview schedule was developed aimed at identifying the perspective of each group on the issues facing people with COPD; the provision of care; barriers to access; service restrictions; functioning of services and service coordination issues.

Data analysis

Transcripts were coded by authors responsible for each study using thematic analysis. In Study 1, coding
disagreements were discussed until consensus was achieved, identifying key themes. This allowed a flexible, evidence-based approach despite the density of the data obtained from the interviews. In Study 2, an initial thematic analysis of Expert Panel 1 was undertaken, identifying four key themes which formed the basis of questions for Panel 2. The results of both panels were then combined and recommendations identified arising from this analysis. In Study 3, data were analysed deductively, and a constant comparative process was used to form broad themes. The themes from all three studies were then compared and collated to identify the final key themes arising from the data.

Ethics approval

Ethics approval for this project was given by the Research Ethics Committees of the Royal Adelaide Hospital and University of Adelaide, Australia.

Results

Study 1

Fifteen people with advanced COPD and eight carers participated in the interviews (Table 1). One participant died before the second interview.

COPD had a devastating impact on these people’s lives, both in terms of physical functioning and social roles. All participants had left the workforce, and no one had private health insurance. Breathlessness meant that basic tasks, such as personal care, cooking and cleaning, were a struggle for all and impossible for many, and activities outside the home were restricted. While home-oxygen enabled participants to remain at home and provided some relief from breathlessness, maintaining oxygen supplies was a source of anxiety, and equipment added to physical restriction and isolation. The sense of panic due to breathlessness was a strong theme.

Participants with carers were concerned about how much their carer did for them, and it was obvious how heavily burdened carers were and how limited respite options were for them. For those who lived alone, social isolation and the challenges of managing day-to-day activities were even greater. Although participants received a range of support from community services, participants were unclear about their entitlements, and those who were aged less than 65 years experienced significant difficulties in accessing many services.

Life for participants with end-stage COPD was inextricably linked with the health system. The most obvious theme from the data was the absence of a clear coordinated pathway to obtaining support and advice. Attendance at GP, specialist and hospital outpatient appointments was difficult, particularly if these were scheduled early in the day. For some, a GP filled the role of care coordinator, but for most, services were experienced as fragmented. Care appeared episodic and reactive, often involving hospitalisation in a crisis. Even in the face of advanced disease with poor prognosis, there was an absence of conversations about future wishes or any advance care planning. Participants described many of their experiences of communicating with health professionals in terms of ‘not being listened to.’ Concerns were also expressed about the level of communication between GP and hospital specialists. The opportunity to discuss their situation, including advance care planning, with the interviewer was welcomed.

The information and skills obtained at pulmonary rehabilitation were valued by the few who were able to complete the programme, but access was difficult and it was apparent that the timing should have been earlier in

<table>
<thead>
<tr>
<th>Participant</th>
<th>Location</th>
<th>Age</th>
<th>Gender</th>
<th>Lived with</th>
<th>MMRC interview 1</th>
<th>MMRC interview 2</th>
<th>AKPS interview 1</th>
<th>AKPS interview 2</th>
<th>QoL interview 1</th>
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</table>

†Referred to a specialist palliative care service. A, alone; AKPS, Australia-modified Karnofsky Performance Status Scale; C, adult child; F, female; M, male; MP, metropolitan; MMRC, Modified Medical Research Council Dyspnoea Scale; N/A, missing data; P, partner; QoL, quality of life measure; R, rural; SR, semi-rural; X, deceased.
The illness. During the course of the study, two participants were referred for specialist palliative care support. This did not include the participant who died before the second interview. All participants recognised that smoking had contributed to their illness and some described a sense of abandonment or judgement from their doctors. Despite the profound changes COPD had wrought in participants’ lives, there was a strong sense of ‘battling on.’ Although some described their life as being over, and some recognised the terminal nature of the illness, they still remained engaged in this day-to-day struggle.

Study 2

The Expert Panel was convened on two occasions (Table 2).

It was evident that there was no easily identifiable transition to end-stage COPD, therefore the original objective of Study 2 was not realised. It was determined that refining morbidity data for policymakers was not possible, nor was it as important as addressing the needs and expectations of people with advanced COPD. All participating health professionals identified that the key issues were to provide support for activities of daily living (ADL), to treat physical and psychological symptoms, to provide better coordination of care and to emphasise the importance of advance care planning as vital for best-practice care.

Study 3

Five focus groups, two interviews and two group sessions were undertaken (Table 2). Thirteen major themes were identified from the data, which were refined to four major themes.

The impact of the trajectory of the illness

The trajectory of COPD, with its acute exacerbations, long periods of relative maintenance and the length of time that people may be seriously ill, has a major impact on service provision, particularly planning and access, as well as on the family and carers.

Access issues

Current levels of services and support for people with COPD were not commensurate with the impact of the illness, and current funding structures do not support care for prolonged periods of time. Despite a willingness by specialist palliative care services to be involved, a lack of flexibility between current service providers considerably disadvantaged people with COPD. Palliative care and home support services were often linked to prognosis rather than need. Clinicians were forced to ‘manipulate the system’ by referring to specialist palliative care services as a means of gaining services and support which would otherwise not be available to patients with chronic disease. Accessing community care options, such as ADL, support was particularly problematic for people aged less than 65 years.

Communication

Communication between health service providers and people with COPD and between health service providers...
themselves was highlighted as a major issue. This was particularly so between the acute care and the primary care sector.

The role of carers

The role of carers was not adequately recognised in the health system nor their need for respite. Consumers, carers and health professionals all emphasised the importance of recognising and addressing the psychosocial needs of people with COPD, as this disease has a major impact on the financial, emotional, mental and physical aspects of life for individuals and families.

Discussion

This project demonstrated that the needs of people with COPD are not being met and that neither respiratory nor palliative care services alone can adequately support people with COPD. An outstanding finding from this research was the consistent and recurring messages that came from all three studies. The Expert Panel and professional focus groups echoed the findings from patients and carers about their unmet needs and the difficulties they faced with remarkable congruence (Table 3).

Care for people with advanced COPD has been focused in the acute care setting with some community support. Care was found to be fragmented, episodic and reactive and did not meet the day-to-day and palliative care needs of these people.

Three key aspects were identified that would improve the care of people with advanced COPD and these should be reflected in all health policy and service provision.

First, the focus of service provision should be on assisting people to live at home. This will require a revision of eligibility criteria for access to community services (e.g. age limitation and performance status) as well as increased recognition of, and support for, carers.

Second, the model of care for people with advanced COPD should be based on the chronic care model, incorporating regular and systematic review, multidisciplinary team care, with coordinated and continuing care. The model must include timely and accurate communication with people with advanced COPD and between all care providers to achieve quality care in a multidisciplinary environment. This research clearly demonstrated the absence of a coordinated pathway for support. Care coordination is pivotal to any new model of care and should occur across hospitals, community and home. The care coordination role should be proactive, supporting as much independence as possible through education and assistance with problem solving but also incorporating the skills and capacity to intervene with more specific assistance when needed.

Third, a key principle of the care model should be the integration of a palliative approach at all phases of the illness. This would foster a person-centred approach, focusing on symptom management and emotional and psychological support, as well as allowing continuing COPD interventions. Health professionals in all areas of chronic disease management require education in palliative care principles and practice.

COPD guidelines and health professional education should emphasise the vulnerability of people with advanced COPD, the symptom burden, in particular dyspnoea and fatigue, the many losses, including changes in role, the impact on relationships experienced by people with this chronic illness and the need for sensitivity and compassion.

A series of recommendations was developed from the data (Table 4). While all the recommendations from this study are grounded in the data from the participants, it is important to note that they are also in line with current health policy and proposed health reforms in Australia.18–22 The National Health and Hospitals Reform Commission recommendations had a specific focus on caring for people at the end of life, urging expansion of access to palliative care services, support for advance care planning and workforce education in this area.20 Palliative Care Australia, the peak body for palliative care in Australia, suggests that seamless, well coordinated care is vital for best-practice care at the end of life and emphasises the importance of care that is patient centred.21 There are also national statements endorsing the importance of patient-centred care,24 support for carers of people with chronic disease25 and for Advance Care Directives,26 all of which are strongly endorsed by the National Palliative Care Strategy.27

Future role of specialist palliative care services

Palliative care services have led the way with their broad ranging, multidisciplinary, flexible approach and will need to continue to lead in embedding a palliative approach in a chronic disease management model. The role of specialist palliative care services will be vital in providing education, consultation, advice and support for respiratory and other clinicians to continue to care for people they may have known for considerable periods of time. Referral to a specialist palliative care service may not be necessary for all people with advanced COPD, but the interface between specialist palliative care and other clinicians will continue to be important in the model of care.

The skills to discuss issues, such as the desired extent of intervention and to sensitively raise end-of-life conversations, are core skills of palliative care clinicians;
Table 3 Comparison of themes from different studies

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
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<tbody>
<tr>
<td><strong>Nature of COPD</strong></td>
<td><strong>Study 3</strong></td>
<td><strong>Recognition of unclear trajectory and length of time involved</strong></td>
</tr>
<tr>
<td>• Limited understanding of COPD, particularly its progressive and terminal nature</td>
<td>• Difficulty defining end of life in COPD</td>
<td>• Chronic disease context emphasised</td>
</tr>
<tr>
<td><strong>Impact of COPD</strong></td>
<td><strong>Study 2</strong></td>
<td><strong>Transport a major issue</strong></td>
</tr>
<tr>
<td>• Physical limitations due to breathlessness</td>
<td>• Importance of ADL support</td>
<td>• High level of needs of people with COPD especially the need for ADL support at home</td>
</tr>
<tr>
<td>• Difficulties with ADL</td>
<td></td>
<td>• Anxiety and depression major problems</td>
</tr>
<tr>
<td>• High levels of anxiety/panic</td>
<td></td>
<td>• Need for spiritual support</td>
</tr>
<tr>
<td>• Social isolation</td>
<td></td>
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<tr>
<td><strong>Access to community services</strong></td>
<td><strong>Study 3</strong></td>
<td><strong>Age under 65 a major barrier to services</strong></td>
</tr>
<tr>
<td>• Uncertainty about access and entitlement to community services</td>
<td>• Use of palliative care referrals to expedite access to community services</td>
<td>• Access to ACAT assessment limited</td>
</tr>
<tr>
<td>• Age barriers to gaining services</td>
<td>• Difficulty in timing of referrals based on uncertain prognosis</td>
<td>• Palliative care input valued, but current model does not support the fluctuating need for services</td>
</tr>
<tr>
<td>• Limited involvement of palliative care services</td>
<td>• Concern about possible number of referrals</td>
<td>• Difficulty accessing hospital admissions by GP</td>
</tr>
<tr>
<td>• Difficulty in accessing GP, specialist and hospital appointments and medications</td>
<td>• Need for diverse range of health workers to meet needs of people with COPD</td>
<td>• Home visiting important</td>
</tr>
<tr>
<td>• Pulmonary rehabilitation access very limited and often too late</td>
<td>• Need for guidelines/checklist approach</td>
<td></td>
</tr>
<tr>
<td><strong>Care coordination</strong></td>
<td><strong>Study 3</strong></td>
<td><strong>Need for continuity and care coordination</strong></td>
</tr>
<tr>
<td>• Fragmentation of care</td>
<td>• Important role for education and self-management</td>
<td>• Coordination could improve management of exacerbations</td>
</tr>
<tr>
<td>• Lack of coordination between hospital and community care</td>
<td>• Need for new coordinated model and access to services</td>
<td>• Links to chronic disease management processes important</td>
</tr>
<tr>
<td></td>
<td>• Call for change in health policy to support care coordination</td>
<td>• Coordination requires knowledge of both respiratory and palliative aspects of care</td>
</tr>
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<td></td>
<td>• Coordination requires knowledge of both respiratory and palliative aspects of care</td>
<td></td>
</tr>
<tr>
<td><strong>Communication</strong></td>
<td><strong>Study 3</strong></td>
<td><strong>Communication between services lacking</strong></td>
</tr>
<tr>
<td>• Difficulty communicating with health professionals</td>
<td>• The importance of communication</td>
<td>• Consumer/health professional communication very poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Burden for carers and lack of support acknowledged</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lack of respite care</td>
</tr>
<tr>
<td><strong>Impact on Carers</strong></td>
<td><strong>Study 3</strong></td>
<td><strong>ACP supported but not done</strong></td>
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<tr>
<td>• Lack of respite care</td>
<td></td>
<td>• Uncertainty about whose role to raise ACP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Concerns about impact on optimism</td>
</tr>
<tr>
<td><strong>Advance care planning</strong></td>
<td><strong>Study 3</strong></td>
<td><strong>Uncertainty about timing</strong></td>
</tr>
<tr>
<td>• Minimal conversations about future wishes</td>
<td>• Palliative care staff skilled in end-of-life conversations</td>
<td>• Judgmental attitudes noted</td>
</tr>
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<td>• Resuscitation conversations only in emergency situations</td>
<td>• ICU should not be site for ACP</td>
<td>• Lack of sympathy for ‘self-inflicted’ condition</td>
</tr>
<tr>
<td>• Support for the idea of ACP</td>
<td>• Need for respiratory examples in ACP guidelines</td>
<td>• Role of outreach nurses emphasised</td>
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<tr>
<td></td>
<td></td>
<td>• Uncertainty about timing</td>
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<tr>
<td></td>
<td></td>
<td>• Cost an issue</td>
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<tr>
<td><strong>Role of smoking</strong></td>
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<td><strong>Uncertainty about timing</strong></td>
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<td>• Role of outreach nurses emphasised</td>
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<td><strong>Home oxygen</strong></td>
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<tr>
<td>• Physical and social limitations</td>
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<td>• Oxygen use contributes to social isolation</td>
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<tr>
<td>• Anxiety about supply and equipment</td>
<td></td>
<td>• Cost an issue</td>
</tr>
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<td>• Cost and rebate issues</td>
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however, they are not perceived as necessary for many other health professionals. Other members of the treatment team for people with COPD need to be supported to develop confident communication skills. A clear finding of this research was that advance care planning discussions were often initiated around the time of an acute exacerbation when both people with COPD and their carers were stressed. This was not appropriate as people could not think clearly, did not have the time to consider the issues and it was too late for many of the planning aspects.

Conclusion

The findings of this research reflect both the international evidence and the Australian context and demonstrate clearly that the healthcare system must change if it is to provide best-practice care for people with advanced COPD and their carers. Neither respiratory nor palliative-care services alone can adequately support people with COPD. There is a need for a flexible model of care that assists these people to navigate the acute healthcare and community support systems, that is patient centred and is coordinated across the primary, acute and community sectors. The integration of a multidisciplinary palliative approach within a chronic disease management strategy, as well as the recognition that active disease management and palliation are complementary, not mutually exclusive, will be central for the best care for people living with advanced COPD.

Acknowledgements

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Haploidentical bone marrow transplants for haematological malignancies using non-myeloablative conditioning therapy and post-transplant immunosuppression with cyclophosphamide: results from a single Australian centre

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Abstract

Aims: To demonstrate safety and efficacy of haploidentical bone marrow transplantation with non-myeloablative conditioning and high-dose post-transplant cyclophosphamide in adult patients with leukaemia or lymphoma.

Background: Human leukocyte antigen haploidentical bone marrow transplantation is a treatment option in patients with haematological malignancies who have no available human leukocyte antigen-matched donor but is limited by conditioning regimen toxicity, graft failure, relapse and graft-versus-host disease (GvHD).

Methods: Twelve patients, median age of 51 years, underwent transplantation with T cell replete bone marrow from a haplotype-matched relative. The conditioning regimen consisted of cyclophosphamide, fludarabine and low-dose total body irradiation. Post-transplant immunosuppression consisted of a single dose of cyclophosphamide 50 mg/kg on day 3, followed by oral tacrolimus and mycophenolate mofetil. Outcomes reported are overall survival, engraftment and chimerism, toxicity, and clinical outcome.

Results: All patients had neutrophil recovery (median 14.5 days), and 11 of 12 had platelet engraftment (median 17 days). Two patients had autologous reconstitution. Seven of nine assessable patients had complete donor chimerism. Four patients had grades II-III GvHD, and none had grade IV GvHD. Four patients developed limited stage chronic GvHD. Five patients with acute myeloid leukaemia relapsed. Two patients died of nonrelapse causes, both from other malignancies, and five patients remain alive and relapse free. Median overall survival was 324 days (range 88–1163).

Conclusion: This regimen is feasible and well tolerated in older patients with high-risk leukaemia or lymphoma, with minimal short-term toxicity and low rates of GvHD. The proportion of disease-free survivors indicates a graft-versus-malignancy effect is present in survivors.

Introduction

Haploidentical allogeneic haematopoietic cell transplantation (HCT) is currently under investigation as a treatment strategy for high-risk haematological malignancies and for those who otherwise lack a suitable donor. The optimum donor for allogeneic HCT is generally regarded as a matched sibling; however, approximately 70% of potential HCT recipients have no sibling donor, and the chance of finding an appropriately matched unrelated donor from international marrow donor registries is highly dependent on ethnicity. Unrelated umbilical cord blood (UCB) banks have increased the number and speed of donor unit availability with less stringent human leukocyte antigen (HLA)-matching requirements but are limited in the adult setting primarily because of inadequate cell dosing, although this may be partly overcome by the use of multiple UCB units. In contrast, every patient shares at least one HLA haplotype with each parent and any children, and has a 75% chance of sharing at least one HLA haplotype with each sibling. The use of HLA-haploidentical related donors would provide virtually all patients with a potential donor irrespective of ethnicity, thus extending allogeneic HCT to over 90% of those who could potentially benefit.
challenges involve overcoming the dual problems of graft-versus-host disease (GvHD) and graft rejection because of HLA disparity.

Several broad approaches to haploidentical HCT have been evaluated. Myeloablative conditioning therapy combined with heavily T cell depleted grafts containing ‘mega-doses’ of CD34⁺ progenitor cells have proved feasible⁶–⁸ but with delayed immune reconstitution and increased infection risk. Non-myeloablative (NMA) conditioning approaches for haploidentical transplantation have also been investigated to reduce conditioning regimen toxicity. One such approach has employed the combination of fludarabine, cyclophosphamide and lowdose total body irradiation (TBI) for conditioning therapy, with an unmanipulated T cell replete bone marrow (BM) graft and post-transplant immunosuppression with high-dose cyclophosphamide.⁹,¹⁰ The rationale for high-dose cyclophosphamide early after transplant is the immunological tolerance conferred by the ability of alkylator therapy preferentially to affect proliferating lymphocytes over resting cells, resulting in deletion of alloreactive T cells. This spares the nonproliferating graft T cells that contribute to immune reconstitution and antitumour activity in the longer term.¹¹,¹² Preclinical studies validated the safety of administering high-dose cyclophosphamide on day 3 post-transplant¹³ and early phase human trials using cyclophosphamide 50 mg/kg on day 3, or both days 3 and 4 have now been published.¹⁰,¹⁴ Using this regimen, Luznik and colleagues¹⁰ demonstrated low rates of graft failure (13%), grades III-IV acute GvHD (6%) and chronic GvHD (cGvHD) (22%).

We have adapted this protocol and report our experience over 2 years in transplanting 12 patients with poor-risk haematological malignancies who lacked matched related or unrelated donors.

**Patients and methods**

**Patients**

Twelve consecutive patients with poor-risk haematological malignancies underwent allogeneic HCT from an HLA-haploidentical related donor at Westmead Hospital from April 2008 to November 2010. All patients gave informed consent for treatment. Patients were considered eligible for haploidentical HCT if no suitable HLA-matched sibling or unrelated donor was available, where autologous HCT was inappropriate and had poor-risk haematologic malignancy. Patient median age was 51 years (range 27–62) (Table 1). Nine patients had acute myeloid leukaemia (AML) with a high risk for relapse on the basis of prior relapse (n = 2), secondary or therapy related AML (n = 2), persistent cytogenetic abnormality following induction chemotherapy (n = 1) or poor-risk cytogenetics (n = 4). Two patients had follicular lymphoma, and one transplanted for progressive disease despite multiple prior lines of treatment and the other with marrow failure following the most recent line of chemotherapy. One patient had chronic myeloid leukaemia (CML) in chronic phase refractory to tyrosine kinase inhibitor (TKI) therapy, with a T315I BCR-ABL mutation (Table 1).

Donors were selected after review of HLA typing data for available family members. Criteria for selection of haploidentical relatives included availability, age, and fitness for marrow harvest under general anaesthesia, cytomegalovirus (CMV) serostatus and ABO blood group matching with the patient. Kir typing was not done.

**Transplant protocol**

The transplant schedule was adapted from that described by Luznik and colleagues.¹⁰ Conditioning therapy consisted of cyclophosphamide 14.5 mg/kg/day ivi + mesna 14.5 mg/kg/day on days –6 and –5, fludarabine 30 mg/m²/day ivi on days –6 to –2, and TBI with a single fraction of 200 cGy on day –1. Donor BM was harvested under general anaesthetic aiming for a minimum total nucleated cell (TNC) count of 2 × 10⁸ per kg recipient weight. In major ABO-mismatched transplants, the graft was red-cell depleted using a Cobe 2991 cell processor (Caridian-BCT, Lakewood, CO, USA). T cell depletion or other manipulation of the marrow was not performed. Monoclonal or polyclonal anti-T cell preparations were not used pretransplant or post-transplant.

Post-transplant prophylaxis against GvHD consisted of cyclophosphamide 50 µg/kg ivi over 60 min on day +3, with mesna 50 mg/kg/day as a 24-h infusion, followed by tacrolimus 2 mg bd po and mycophenolate moletil (MMF) 15 mg/kg/dose tds po starting on day +4. In the absence of GvHD, MMF was weaned from day +30 and tacrolimus from day +84.

**Supportive care**

Granulocyte colony-stimulating factor 5 mg/kg/day was administered from day +4 until neutrophil recovery >1.0 × 10⁹/L. Infection prophylaxis was as standardly used at our institution for related allogeneic transplants and consisted of ganciclovir 5 mg/kg bd days –8 to –1 in those recipients who were CMV seropositive, cotrimoxazole 160/800 mg bid from day –8 to day –1, metronidazole 400 mg po tds, ciprofloxacin 750 mg bd, acyclovir 800 mg bd, and fluconazole 400 mg starting day 0. Penicillin V 250 mg bd and cotrimoxazole 160/800 mg bid twice weekly were commenced on day +28.
Chimerism analysis
Flow-sorted peripheral blood T cells or peripheral blood mononuclear cells (PBMC) were analysed for chimerism using polymerase chain reaction (PCR) on highly polymorphic short-tandem repeat (STR) markers. Complete engraftment was defined as the lack of recipient-specific STR on polyacrylimide gel analysis, with mixed chimerism detectable when greater than 5% recipient STR present. In one patient with a sex-matched graft and without an informative STR marker, graft rejection was confirmed by HLA typing on PBMC.

Statistical methods
Engraftment and survival were analysed using the method of Kaplan–Meier. Survival outcomes were estimated using a close-out date of 30 June 2011.

Results
BM grafts
Details of the HLA matching, donor source and cell doses are shown in Table 1. Donors were either siblings (n = 9) or children (n = 3). HLA matching at HLA-A, -B and -DRB1 was either 3/6 (n = 11) or 4/6 (n = 1). The median BM TNC count was $3.05 \times 10^8$/kg, (range 2.4–5.7), and median CD34+ dose infused was $2.55 \times 10^6$/kg (range 1.3–4.8).

Engraftment and chimerism
All 12 patients had sustained neutrophil recovery to >0.5 x 10^9/L at a median time of 14.5 days (range 4–55). One patient failed to reach a platelet count >20 x 10^9/L prior to death from relapse, and the remainder showed platelet recovery at a median of 17 days post-transplant (range 1–66). Five patients did not reach nadir platelet counts ≤20 x 10^9/L. One patient required no platelet transfusions, and three others avoided both red cell and platelet transfusions.

Chimerism status was assessable in nine patients. Two patients had early relapse, and no post-transplant chimerism testing was performed. One patient had no informative STR marker available, and autologous reconstitution was demonstrated by repeat HLA typing. One patient had 90% donor T cell chimerism at day 31, but subsequent autologous reconstitution was shown on day 73, while another had persistent mixed chimerism to day 123, then relapsed. The remaining seven patients achieved complete donor T cell chimerism.
Transplant toxicity

The procedure was well tolerated, with all patients surviving to discharge and no patients requiring intensive care unit admission or parenteral nutrition. No patients experienced hepatic sinusoidal-oblstructive syndrome, haemorrhagic cystitis or grades III-IV mucositis. The median length of hospital stay was 25 days (range 11–52). Bacteriaemias post-transplant were detected in four patients (33%), central line-related coagulase negative staphylococcus in three cases and a skin contaminant bacillus species in the other case, but no patients developed septic shock or required inotropic or ventilator support. Only three out of nine at-risk patients required pre-emptive CMV therapy, all with a complete response. There were no proven or probable invasive fungal infections, although one patient was treated for aspergillus on the basis of a sputum isolate in the absence of computed tomography chest signs (Table 2).

Four out of 12 patients developed grades II–III acute GvHD, all responding to corticosteroids and tacrolimus, but no patients experienced grade IV acute GvHD. Limited stage cGvHD occurred in 4 out of 11 evaluable patients, with no patient developing extensive cGvHD.

Transplant-related mortality at 1 year was 16%, with both patients dying from secondary malignancy at 220 and 256 days post-transplant.

Relapse

Overall, five patients had relapse of their haematologic malignancy, all with AML. Four subsequently died of relapse, while the other died in complete remission (CR) 2 from acute GvHD following UCB transplantation.

Survival

With a median follow up of 685 days post-transplant (minimum follow up 231 days), the median overall survival for the group is 324 days (range 88–1163) (Fig. 1). The cumulative incidence of mortality at day 100 is 8%, with one patient succumbing to relapse after 88 days, while the mortality at 1 year is 50% (5 of 10 evaluable patients), with three dying of relapse and two of secondary malignancies. Five of 12 patients are alive and relapse free, with median follow up of 384 days (range 231–1163).

One patient was transplanted for TKI refractory CML in chronic phase with a T315I mutation. Dasatinib was ceased on day –9. Baseline quantitative PCR for BCR-ABL was 11.2%, but by day 31, the level had reduced to 0.0027% and was undetectable at day 76. She remains in complete molecular response with undetectable BCR-ABL and no GvHD after a follow up 384 days.
Discussion

This report demonstrates the feasibility of the use of unmanipulated T cell replete BM transplantation from HLA-haploidentical related donors following a reduced-intensity conditioning (RIC) regimen in a group of patients with high-risk haematological malignancies. The use of a high dose of cyclophosphamide following infusion of the donor BM to deplete alloreactive donor T cells enabled stable engraftment in the majority and prevented serious GvHD – obviating the need for T cell depletion of the graft and reducing the risks of immunosuppression and infection. The regimen was well tolerated, with minimal mucositis and no serious bacteremias, enabling its use in older patients who lacked matched related or unrelated donors and for whom a myeloablative unrelated cord blood transplant was contraindicated. In addition, because it requires no graft manipulation or in vivo T cell depletion, it is simple, less costly and practical to implement, particularly where cost constraints may apply.

Our results are consistent with the reported experience from the USA using the same regimen. Seventeen percent (2 out of 12) of our patients had graft loss and autologous reconstitution compared with 20% (2 out of 10 patients) in the original phase 1 trial reported by O’Donnell and colleagues and 14% (9 out of 66 patients) in the subsequent report by Luznik and colleagues.

The overall cumulative incidence of relapse in our cohort is 42% (5 of 12 patients) and nonrelapse mortality is 17% (2 of 12 patients) compared with that of Luznik et al. of 51% and 15%, respectively, at 1 year. The risk of post-transplant relapse is strongly influenced by pretransplant disease type and status. Two of our patients relapsed early post-transplant, both with advanced AML. Given the relatively low intensity of the conditioning regimen, this protocol may not be appropriate for patients at high risk of early relapse. We are implementing a modified protocol using a more intensive conditioning regimen using fludarabine and intravenous busulfan for such patients.

Two patients died while in remission of their haematological malignancy from other malignancies. One patient had a malignant melanoma resected several years previously with no evidence of recurrence, but presented with an aggressive metastatic melanoma post-BCT. The other patient had been a heavy smoker for many years and succumbed very rapidly with multiorgan failure at approximately 7 months post-transplant. Post-mortem examination subsequently revealed wide-spread adenocarcinoma of probable lung origin. It is highly likely that both malignancies were present prior to transplant, and it is possible that their presentation was hastened by the post-transplant immunosuppression.

One of our patients was transplanted for TKI refractory CML with a T315I mutation. Allogeneic transplantation results have been published in this group with long-term survivors reported. Our early results with a haploidentical family donor are encouraging, with a complete molecular response from day 71 and no significant GvHD to date. In the absence of an alternative novel agent, clinical trial or suitable matched donor, this approach may be a viable alternative in this patient group without other options.

The choice of haploidentical donors or unrelated UCB units for allogeneic transplantation where no HLA-matched donor is available is currently being questioned. Parallel phase 2 studies of haploidentical and double UCB transplantation were recently published. The outcomes of haploidentical transplantation using NMA conditioning and post-transplant cyclophosphamide were equivalent to RIC UCB in terms of survival and GvHD rates, and indeed were comparable with registry outcomes for HLA-matched RIC HCT. The outcomes of unrelated UCB transplantation using myeloablative conditioning at our institution have been published. For UCB transplants, 5 out of 11 patients died within 2 months post-transplant from transplant-related complications, largely as a result of prolonged time to neutrophil engraftment, and there did not appear to be a significant improvement in survival using two versus one UCB units. Our results for haploidentical RIC HCT appear safer, and given the ease and speed of identifying haploidentical relatives, and the
contrasting expense and complexity of unrelated cord blood searches and procurement, this approach seems more amenable, particularly to older high-risk patients.

**Conclusion**

We report the outcome for 12 patients with poor-risk hematologic malignancies having haploidentical allogeneic HCT, demonstrating low rates of transplant morbidity in terms of infections and GvHD, low NRM, and acceptable rates of graft failure and relapse in this high-risk cohort. This reduced intensity haploidentical approach appears simple and feasible, and extends the availability of a potentially curable treatment in a patient group with limited therapeutic options. Additional measures, including outpatient conditioning, modification of conditioning regimen dosing, post-transplant donor lymphocyte infusion or the use of peripheral blood stem cell rather than BM (which is under investigation in our institution) may be necessary to improve outcomes in patients at high risk of relapse.

**References**

Improved survival trend of patients with hepatocellular carcinoma at an Australian tertiary hospital between 1995–2009

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Abstract

Aim: To evaluate trends in survival of patients with hepatocellular carcinoma (HCC) at The Alfred over a 15-year period from 1995–2009


Results: The study population consisted of 215 patients; 110 diagnosed between 1995–2001 (Cohort A) and 105 between 2002–2009 (Cohort B). Overall survival increased significantly between 1995–2010 (P = 0.016); median survival was 365 days in Cohort A compared with 665 in Cohort B. The improvement in survival was associated with an increase in the proportion of cases detected at an asymptomatic stage (P = 0.012), a decline in the severity of liver disease at diagnosis (P = 0.002) and increased utilisation of loco-regional therapy (P = 0.001) over the same period. Survival of patients detected through screening was significantly higher than those detected through non-screening methods (1309 vs 233 days, P < 0.001).

Conclusions: The survival of patients with HCC managed at a tertiary referral centre has improved over the period 1995–2009. This improvement may relate to the increased detection of the disease at an asymptomatic stage (e.g. through screening) as well as increased utilisation of effective loco-regional therapies for HCC.

Introduction

Primary liver cancer or hepatocellular carcinoma (HCC) is a significant disease burden being the fifth most common cancer and the third most common cause of cancer deaths worldwide.1 Mortality rates of HCC are notoriously high with 5-year survival rates a low 3–5%.2

The incidence of HCC varies by geographical location according to the prevalence of strongly associated risk factors, such as hepatitis B virus, hepatitis C virus, alcohol and non-alcoholic steatohepatitis. In Australia, the incidence and mortality rates of HCC have increased since the 1970s,3 alongside a changing epidemiology – with an increase in viral associated HCC.4

Coincident with these developments has been a shift in the clinical approach to HCC. In addition to the introduction of screening for HCC in at-risk populations, HCC management has evolved over the last two decades to incorporate a number of curative (liver resection, transplantation and local ablative therapies, including radio-frequency ablation (RFA) and percutaneous ethanol injection (PEI)) as well as non-curative therapies (transarterial chemo-embolisation (TACE) and sorafenib) that are associated with improved patient survival.5,6 While the overall effect of these changes has yet to be delineated in an Australian population, improved survival has been noted in overseas populations.6,7 However, these outcomes are limited to registry-based studies and do not correlate survival outcomes with clinical practice developments. This study aimed to document trends in the survival of Australian patients with HCC and identify associated changes in the clinical approach to HCC.

Methods

Study design

This was a retrospective cohort analysis of all patients with HCC from The Alfred, Melbourne, Australia
between January 1995 and December 2009. Patients entered into the study were identified from a comprehensive database maintained by The Alfred Gastroenterology Department. In all patients, a diagnosis of HCC was achieved through histocytological analysis or through imaging, demonstrating a diagnostic contrast enhancement pattern on triple-phase helical computed tomography (CT) and/or magnetic resonance imaging (MRI) liver as previously described.\(^1\)

Data were collected retrospectively from patients’ medical records, including demographics, epidemiology, aetiology and severity of liver disease, mode of HCC detection (screened, symptomatic or incidental), tumour characteristics and treatment modalities. Patients were classified as ‘screened’ if disease was detected at an asymptomatic stage by surveillance imaging (i.e. ultrasound or CT scan) and/or alphafetoprotein (AFP) levels.\(^2\) Severity of liver disease at diagnosis was assessed by liver function tests, platelet count and international normalised ratio with the Child–Pugh (CP) grade calculated. The presence of portal vein thrombosis was determined based on radiological evidence. Tumour parameters (number of nodules, maximum diameter of tumour, the presence of vascular invasion and extrahepatic spread) were obtained from radiological (ultrasound, dynamic CT/MRI) reports. Tumours were staged according to the Cancer of the Liver Italian Program (CLIP) staging system.

Treatments used included hepatic resection, liver transplantation, RFA, PEI, TACE and sorafenib. Treatments were classified as curative (resection, ablation or transplantation) and non-curative (TACE, sorafenib, clinical trial agents or palliative care) and subclassified as locoregional (local ablation, TACE) and surgical (resection, transplantation). Dates of death were obtained from hospital/general practitioner medical records and the Victorian Cancer Council Registry. The survival period was calculated as the time between date of diagnosis and date of death. Patients alive at the end of the study period were censored on 1 August 2010.

**Statistical analysis**

Baseline data were presented as mean ± standard deviation for quantitative variables, and frequencies and percentages for qualitative variables. Patient survival periods were reported as median values. The study population was divided according to the period of diagnosis: Cohort A, diagnosed between 1995–2001 and Cohort B between 2002–2009. Differences over time were analysed using Spearman’s test for correlation. Patients were also divided according to method of detection (i.e. screening and non-screening methods), with comparisons made using the Pearson Chi-squared test for categorical data and the Mann–Whitney U-test for non-parametric continuous data. Kaplan–Meier survival curves were generated and compared using log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to analyse the prognostic relevance of baseline and treatment covariates with covariates with a P-value less than 0.05 on univariate analysis entered into multivariate analysis. Results were presented as the hazard ratio + 95% confidence interval, with P-value from the WALD test. All significance tests were two-tailed, with a P-value of 0.05 considered statistically significant. Data analysis was performed using statistical software SPSS 16.0 (SPSS, Chicago, IL, USA).

**Results**

**Patient characteristics**

Between January 1995 and December 2009, 215 patients were diagnosed with HCC at The Alfred. Baseline demographic and clinical characteristics of the overall study population are shown in Table 1. The mean age of the total cohort was 63.8 years, with male patients significantly younger than females at diagnosis (63 ± 11 vs 68 ± 9 years; \(P = 0.001\)). Cirrhosis was present in 88% of patients, with alcohol as the predominant primary aetiology of liver disease as well as a disease cofactor in 38% of patients with hepatitis C and 19% of those with hepatitis B. Of the 215 patients, 110 (51.1%) were grouped in Cohort A (diagnosed between 1995–1999) and 105 (48.9%) in Cohort B (2002–2009). The two cohorts were similar with respect to gender, age and aetiology of liver disease, as shown in Table 1. However, there was an increase in the frequency of presentation at an asymptomatic stage over the two cohort periods (40.7% vs 58.5%; \(P = 0.012\)), including a non-significant increase in the proportion of cases detected by screening (31.8% vs 38.3%; \(P = 0.31\)). In addition, the severity and activity of liver disease at diagnosis declined over time as assessed by CP class (\(P = 0.004\)) and serum alanine aminotransferase (ALT) levels respectively \((P = 0.01)\). No significant difference was observed in any of the tumour parameters, AFP levels and mean CLIP score across the two cohorts. While the rate of curative therapies was unchanged over the two diagnosis periods, a significantly higher proportion of patients received loco-regional therapy in Cohort B compared with Cohort A \((P = 0.001)\). This included a higher use of local ablative therapies \((P = 0.07)\), including RFA \((P < 0.001)\), as well as TACE \((P = 0.014)\) (Table 1).
Survival trends

At the time of analysis, 155 (72.1%) of patients had died, and 35 (16.3%) were still alive, with the survival status unable to be ascertained in 21 (10.1%) patients. The median survival of the overall cohort was 396 days, with survival rates of 1, 3 and 5 years of 53.0%, 18.3% and 10.9% respectively. Median survivals were significantly different between Cohorts A and B, being 365 and 665 days respectively ($P = 0.016$) (Fig. 1).

Predictors of survival

Several factors predicted survival on univariate analysis, including gender and those related to diagnosis (time period of diagnosis, method of detection), liver disease
(serum alkaline phosphatase (ALP); CP class) and tumour burden (number of nodules, greatest tumour diameter, presence of vascular invasion/extrahepatic spread, elevated AFP, portal vein thrombosis and CLIP stage) (Table 2). On multivariate analysis, independent factors associated with survival were gender, time period of diagnosis, detection by screening, ALP levels, CP class, greatest tumour diameter, extrahepatic spread and portal vein thrombosis (Table 2).

**Effect of screening**

Patients who had the disease detected by screening had a significantly higher median survival than those detected by non-screening methods (917 vs 253 days, \( P < 0.001 \)) (Fig. 2). In addition, screened patients had more favourable tumour characteristics at diagnosis, including smaller tumour diameter (mean 3.08 cm vs 6.48 cm, \( P < 0.001 \)) and lower frequency of vascular invasion (4.3% vs 26.2%, \( P < 0.001 \)), and extrahepatic spread (4.3% vs 13.4%, \( P = 0.046 \)). A higher proportion of screened patients was treated with curative intent (68.1% vs 29.9%, \( P < 0.001 \)) compared with non-screened cases.

### Table 2 Predictors of overall survival on Cox regression modelling

<table>
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<th>Parameter</th>
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<th>Multivariate analysis</th>
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<td></td>
<td>HR</td>
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<td>Gender (female vs male)</td>
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<td>Diagnosis group (A/B)</td>
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<td>Number of nodules</td>
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<td>Presence of vascular invasion</td>
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<td>Extrahepatic spread</td>
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<tr>
<td>CLIP score</td>
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AFP, alphafetoprotein; CI, confidence interval; CLIP, Cancer of the Liver Italian Program; HR, hazard ratio.
Discussion

In this study, we report a significant improvement in the survival of HCC patients diagnosed at an Australian tertiary hospital over the period 1995–2009. The improvement occurred over the last decade, with higher median survivals observed in cases diagnosed between 2002–2009 compared with 1995–2001. Notably, the survival trend appears real with the diagnosis period an independent predictor of survival on multivariate analysis. Several prognostic factors were identified that correlated with the improvement in survival over time. These included an increase in the proportion of asymptomatic cases at diagnosis, such as through screening, a reduction in the severity of liver disease at diagnosis and increased utilisation of loco-regional therapies, including local ablation and TACE.

Our study findings support the now common clinical practice of screening at-risk patients for HCC. We found that detection through screening is associated with a significant survival benefit and is predictive of survival on multivariate analysis even when confounding factors, such as tumour characteristics and severity of liver disease, are included. Of note, the proportion of patients diagnosed by screening increased from 32% to 39% over the two cohort periods. While this increase was not significant, there was an increase in the number of cases presenting at an asymptomatic stage (i.e. through screening and incidental imaging finding) that is known to be associated with a better prognosis.1–8–15

Several data, including a large randomised controlled trial, indicate that HCC screening does confer a survival advantage.16–20 Consequently, practice guidelines developed by learned societies now recommend patients at high risk for HCC be entered into surveillance programmes (Level I evidence).20,21 These high-risk groups include those with cirrhosis and hepatitis B carriers, and in particular, Asian males over 40 years, females over 50 years and those with a family history of HCC. HCC surveillance should be performed using ultrasound (Level II) with or without AFP measurement with patients screened at 6 monthly intervals (Level II).20,21

HCC prognosis is determined by both tumour burden and degree of liver dysfunction. Although we observed no change in tumour characteristics over time, there was a reduction in the severity and activity of liver disease over the two cohorts, as reflected by the improvements in the CP grade and serum ALT levels at diagnosis respectively. This might reflect improvements in the management of liver disease over the past decade, such as the increased use and availability of potent antiviral therapies for hepatitis B and C. In addition, it might relate to the increased detection of HCC at an asymptomatic stage, including the impact of screening, particularly given that screened patients are more likely to have less advanced liver disease.14 Regardless, the reduction in liver disease severity is a possible contributor to improved patient survival, given the importance of liver function as a prognostic determinant.

Patients with early stage HCC are amenable to treatment with potentially curative therapies, including hepatic resection and transplantation, while those with unresectable disease are suitable for loco-regional therapy with local ablation and/or TACE. Over the study period, we found a non-significant 10% increase in the proportion of patients treated with curative intent. There was, however, a significant 75% increase in the rate of utilisation of loco-regional therapy between the first and second cohort periods, that included a significant 2.5-fold increase in the frequency of performing TACE. As TACE improves the overall survival of patients with unresectable HCC,22 it is likely that this additional therapy contributed in part to improved patient survival. Moreover, the preferred method of ablative therapy changed over time, with a significant increase in the use of RFA and declining use of PEI for those with early stage disease. This trend is consistent with recent evidence showing that RFA confers a greater survival benefit than PEI.23–27 Thus, it seems reasonable, based on the earlier data, to hypothesise that improved survival was in part due to trend developments in the treatment of HCC.

There are several caveats to consider when interpreting these results. First, being a retrospective study, the observed changes in clinical practice and survival outcome may be coincidental, rather than reflect a true correlation. Second, because the study population was relatively small, at least by world standards, there is an increased chance of missing statistically significant trends and more subtle changes upon survival benefit. Still, compared with previous Australian studies, our cohort size is significant, with only one other having more than 200 patients.15 Third, our study was drawn from a single centre with a special focus on liver disease, and therefore, it is possible that selection bias influenced the results. However, several factors suggest otherwise. Notably, our results are supported by current understanding of HCC management with The Alfred archetype of a number of other tertiary institutions in Australia that provide patients with appropriate access to a broad range of HCC therapies. In addition, analysis of regional municipal council records showed that our local population was diverse in background, age and socio-economic status.28 Hence, the correlation of clinical trends and survival is unlikely to relate to population selection bias. Nevertheless, larger studies should be performed on a multicentre
and/or interstate basis to confirm the extent to which the results can be generalised.

Over the next decade, several opportunities exist to improve further the survival of patients with HCC. These include initiatives to promote the education, adherence and uptake of screening/surveillance programmes that should now be routinely implemented in at-risk patients. In addition, further advances in therapy are expected particularly for those with intermediate and advanced disease. For example, sorafenib is under evaluation as an adjuvant therapy in early and intermediate-stage disease, while several oral chemotherapeutic agents are currently in clinical development, among which are agents targeted at subjects with disease progression or intolerance to sorafenib. Last, the referral process to established multidisciplinary teams at major hospitals needs to be streamlined and additional funding made available to support multidisciplinary meetings in order to optimise the management and by inference survival of HCC patients.

**Conclusion**

This study demonstrates a significant improvement in survival of patients with HCC diagnosed and managed at an Australian tertiary hospital over the period 1995–2009. This survival trend improvement correlated with increased detection at an asymptomatic stage, improved liver function at diagnosis and an increasing application of loco-regional therapies, including TACE. These findings provide positive affirmation of the changing clinical approach to HCC.

**References**

Triple negative breast cancer in a male-to-female transsexual

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Key words
breast cancer, transgender, hyperprolactinaemia, oestrogen, antipsychotic.

Abstract
There is limited published literature on the risk of breast cancer in transgender patients. We report a case of an aggressive triple negative inflammatory breast cancer in a male-to-female transsexual. This patient had a complicated psychiatric history with significant antipsychotic use, and the case raises several questions about the pathogenesis of this breast cancer. The literature on breast cancer in transgender patients and in relation to hyperprolactinaemia is reviewed.

A 43-year-old, male-to-female transsexual was found to have a painful, erythematous left breast with a palpable mass on examination in July 2010 when she presented after an overdose of amisulpride. Prior to this, she had been on antibiotics for 1 week prescribed by her general practitioner. She described no systemic symptoms at this time. She was referred to a breast clinic, and at this review it was also thought that infection was present. There was, however, no improvement with antibiotics. Her case was reviewed in a multidisciplinary meeting approximately 4 weeks after her first presentation, when she was described as having a 10 × 10 × 8 cm central thickening of her left breast. A clinically enlarged left axillary node was now present. Histology from core biopsy was consistent with an invasive ductal carcinoma, at least grade 2, with lymphatic involvement. Immunohistochemical studies revealed no staining for oestrogen receptor, progesterone receptor or HER2. Staging computed tomography (CT) and bone scans were both normal.

She was first seen in oncology outpatients in September of 2010. At her first assessment, a prolactin level was checked and was greater than five times the upper limit of normal. Review of her records showed that this had been elevated to similar levels in the past, dating back to 2005. She commenced dose-dense doxorubicin, cyclophosphamide neoadjuvant chemotherapy, which was followed by dose-dense paclitaxel chemotherapy.

Funding: None.
Conflict of interest: None.
The patient’s history of gender identity disorder spanned several years. She had initially started taking cross-sex hormones in 1995, with conjugated oestrogen and cyproterone acetate, and she continued this consistently until 2002. Her use of cross-sex hormones was then erratic for 3 years, becoming consistent again from 2005 when she recommenced cyproterone (50 mg) and oestradiol valerate (2 mg BD). Spironolactone (200 mg OD) was substituted for cyproterone in 2006 because of concerns that this may have been worsening her depression. She underwent gender reassignment surgery in Thailand in March 2010, and never had breast augmentation.

This patient had significant psychiatric comorbidities, with multiple episodes of self-harm from the age of 25, and was considered to have a chronic high risk of completed suicide. She had several psychiatric diagnoses assigned to her, including borderline personality disorder and major depressive disorder, with her depressive symptoms controlled by use of multiple medications, including antipsychotics. Risperidone, olanzapine, quetiapine, clonazepam, methotrimeprazine and fluoxetine had been used at various times in the 10 years prior to this presentation. She was commenced on amisulpride in May of 2010. At commencement of chemotherapy, her other medications included quetiapine, doxepin, zopiclone and spironolactone. Her oestradiol had been stopped 2 weeks prior to her first oncology appointment. She had no family history of breast or ovarian cancer.

She completed her chemotherapy in January of 2011, with clinical improvement in the breast. Unfortunately, she presented to the emergency department with chest pain later during the same month. A CT pulmonary angiogram was undertaken, and showed bony metastases in the spine and sternum. A bone scan confirmed these findings. A planned mastectomy was, therefore, not undertaken, and she proceeded to breast radiotherapy for local control.

She was found dead at her own home in March of 2011. Autopsy confirmed cause of death as an overdose of doxepin, but also noted extensive metastatic tumour deposits in the liver secondary to her primary breast carcinoma.

Breast cancer in transgender patients appears to be rare. A review of the literature revealed seven cases of breast cancer in male-to-female transsexual patients, described to varying degrees.1–6 Of the four cases that describe oestrogen receptor status, three cases are negative and one positive on immunohistochemistry. The reported cases include one case of breast cancer in a cohort of 2236 Dutch male-to-female transsexuals, cumulative over 30 years.1 However, as discussed by Gooren et al.,1 it is likely that there is underreporting of long-term complications of cross-sex hormone use, and there will be strong variation in oestrogen exposure of the patients in this cohort, making risk assessment difficult. The lack of reported cases is likely contributed to by several reasons, in addition to underreporting, including that transsexualism is rare, and that the prevalence of hormone-dependent tumours, such as breast and prostate cancer, is low.7 The historical use of cross-sex hormones may have been too short for any malignancies caused by these to be apparent, with the first documented hormone treatments of transsexuals beginning in the 1970s.1

Prolonged exposure to oestrogen is known to be a risk factor for developing breast cancer, with early menarche and late menopause both associated with increased risk of breast cancer in genetic females.8 Hormone replacement therapy (HRT) has also been implicated as increasing risk of breast cancer in genetic females, with results from the Woman’s Health Initiative reporting increased risk for combined oestrogen and progesterin HRT.9 A more recent prospective study has also shown greater risk for combined HRT than oestrogen-only formulations, and that the risk of breast cancer development was greater if HRT was initiated around menopause compared with later.10 Transgender patients often use cross-sex hormones for longer periods of time than genetic females and often at significantly higher doses. It is unknown whether this is safe, or as safe as, administration of long-term sex-appropriate steroids.

The origin of oestrogen receptor-negative breast cancer is under debate, with the possibilities including evolution from oestrogen receptor-negative stem cells and development from oestrogen receptor-positive precursors.11 Whether our patient’s cross-sex hormone use contributed to the development of her cancer is unknown. The immunohistochemistry of her core biopsy indicates that her tumour was not sensitive to the use of oestrogen, as it was hormone receptor-negative, but in the absence of a family history of breast cancer, it is possible that her use of cross-sex hormones may have had an impact on the development of her cancer. Her medical history suggests other possible contributing factors to the development of her cancer, in particular her hyperprolactinaemia.

Increased prolactin levels have been demonstrated in male-to-female transsexuals using oestrogen and cyproterone.12 The long-term consequences of hyperprolactinaemia are not well understood, but there is now laboratory-based evidence that prolactin may be a tumour promoter in humans for breast and prostate tissue.13 In clinical studies, plasma prolactin levels have also been correlated with subsequent risk of breast cancer in postmenopausal and premenopausal women,14–16 and a retrospective cohort study of more than 52,000 women...
exposed to prolactin elevating dopamine antagonists found a 16% increase in the risk of breast cancer for those exposed to dopamine antagonists compared with those not exposed, with a dose–response relationship between cumulative doses and greater risk. This risk was seen both in antipsychotic dopamine antagonists, for example risperidone, and prolactin elevating antihistaminic dopamine antagonists, such as metoclopramide. Any antipsychotic can elevate prolactin, although the frequency and severity differ between the various antipsychotics, with the highest rates of hyperprolactinaemia reported in association with risperidone and amisulpride. The patient described in this case had been on antipsychotics for several years and had documented hyperprolactinaemia. This may also have contributed to her development of breast cancer.

This case highlights several issues for transgender patients. This includes the lack of knowledge about the risks of long-term cross-sex hormone use and also the risks of hyperprolactinaemia in the development of breast cancer. Cessation of cross-sex hormones would result in loss of female characteristics, which is likely to be unacceptable to most transgender patients. Until further research into the risks of developing breast cancer is undertaken, decreasing the dose of oestrogen to the lowest possible for maintenance should be considered. For patients on antipsychotics, further research is needed as to whether routine screening of prolactin levels would be helpful. Physicians caring for transgender patients need to encourage them to participate in the relevant cancer screening protocols, which for breast cancer screening for male-to-female transsexuals is the same as the guidelines for biological women. Further reporting of cases such as the one discussed earlier should be encouraged as the current literature pertaining to the risks of breast cancer from cross-sex hormone use and hyperprolactinaemia is sparse.

References

Diphtheria is an acute, highly infectious, vaccine-preventable and previously endemic disease whose etiologic agent is \textit{Corynebacterium diphtheriae}. Diphtheria may manifest as an upper respiratory tract infection, a cutaneous infection or as an asymptomatic carrier state. The most common sites of infection are the pharynx and the tonsils, with common clinical manifestations that include sore throat, malaise, cervical lymphadenopathy and low-grade fever. Absorption and dissemination of \textit{C. diphtheriae} from the respiratory tract can cause disseminated infection and may lead to cardiac or neurological toxicity. The cornerstone of treatment for diphtheria is diphtheria antitoxin. Early treatment is critical as the degree of protection is inversely proportional to the duration of the illness before its administration. Routine childhood vaccination virtually eliminated diphtheria in most industrialised countries. However, in the pre-vaccination era, diphtheria was the most common infectious cause of death in Australia. A case of diphtheria in Brisbane in April 2011 and two recent positive cultures in regional Victoria underscore the need for heightened awareness of \textit{C. diphtheriae} as an important pathogen. In order to prevent the re-emergence of diphtheria in Australia, public health measures are required to increase immunity in early school leavers and the adult population, and to ensure that travellers to endemic regions are fully immunised. Health policy-makers and clinicians alike should not underestimate the importance of primary vaccination and booster vaccination against diphtheria among healthy adults and travellers.
Corynebacteria are Gram-positive rods that have a 'club-shaped' appearance.\(^2\) *C. diphtheriae* is a non-sporulating, unencapsulated, non-motile and pleomorphic bacillus that is subdivided into four biotypes: gravis, mitis, intermedius and bellanti.\(^1\) These subtypes are classified on the basis of differing colonial morphology, fermentation reactions, haemolytic potential and severity of the resulting disease.\(^2,7\) Although the diagnosis of diphtheria is largely clinical, definitive diagnosis can be achieved by isolating and identifying *C. diphtheriae* from the infected site utilising a selective culture medium containing potassium tellurite.\(^8\) Definitive diagnosis also requires toxin detection by PCR to confirm a toxigenic strain; PCR has largely replaced the Elek immunoprecipitation test.\(^9\) However, pitfalls in the diagnosis of diphtheria exist as most laboratories rarely attempt to isolate *C. diphtheriae*, and thus may not stock the required media.\(^8\)

The major virulence factor of *C. diphtheriae* is its potent exotoxin.\(^2\) Exotoxin production is dependent on the presence of a lysogenic β-phage, which carries the gene encoding the toxin (tox+).\(^2\) Strains of *C. diphtheriae* that lack the lysogenic phage do not produce toxin; however, they can be converted to the toxigenic strain both in the laboratory and in nature.\(^2,6\) If non-toxigenic bacilli are infected with the bacteriophage from toxigenic bacilli, the offspring are lysogenic and toxigenic, and these traits are hereditary.\(^7\) Thus, although the frequency of carriage of tox+ lysogenic *C. diphtheriae* is low in industrialised countries, there is a risk that tox− strains could become lysogenised by introduction of a tox+ strain from developing countries where diphtheria is endemic.\(^2\)

Humans are the only known reservoir for *C. diphtheriae*.\(^2\) The primary mode of spread is through airborne respiratory droplets, direct contact with respiratory secretions or direct contact with exudate from infected cutaneous lesions.\(^2\) Cutaneous carriage of *C. diphtheriae* is an important reservoir of person-to-person spread of this pathogen in areas where herd immunity is low.\(^10\)

Following an incubation period of 2–4 days, local signs and symptoms of inflammation develop at various sites within the respiratory tract, such as the anterior nasal, tonsillar, laryngeal and tracheobronchial regions.\(^2\) The most common sites of infection are the pharynx and the tonsils, with clinical manifestations that include sore throat, malaise, cervical lymphadenopathy and low-grade fever.\(^1\) Hoarseness, dyspnoea, cough and stridor can result from laryngeal involvement. In many cases, formation of a coalescing pseudomembrane occurs on the tonsils, tonsillar pillars, uvula, soft palate, oropharynx or nasopharynx.\(^8\) This membrane initially appears glossy and white, and may develop into a grey colour with green or black patchy necrosis,\(^2\) and the extent of the membrane correlates with the severity of the symptoms. More specifically, involvement of the posterior pharynx, soft palate and periglottal areas is associated with cervical adenopathy and oedema of the submental and anterior cervical areas, which can result in respiratory stridor, respiratory insufficiency and death.\(^2,12\) In uncomplicated cases, the ‘bull-neck appearance’ resolves within approximately 2 weeks; however, *C. diphtheriae* can disseminate from the respiratory tract and cause systemic infection.\(^2\)

Cutaneous infections occur primarily in people who live in the tropics but have also been reported within disadvantaged populations in industrialised countries, such as alcoholics, intravenous drug users and the homeless.\(^7,11\) Cutaneous diphtheria can be caused by both toxigenic and non-toxigenic strains of *C. diphtheriae*. The presenting lesion is usually an ulcerative lesion, ‘eczema diphtheriticum’, which usually appears on the lower legs, feet or hands.\(^12\) Individuals with cutaneous diphtheria have a low risk of developing the pharyngeal form of the disease and the toxic manifestations.\(^10\)

Absorption and dissemination of *C. diphtheriae* from the respiratory tract can cause disseminated infection,\(^1,2\) however, the most feared complications arise from the toxin’s effects. The risk of toxic complications is inversely proportional to the number of diphtheria toxoid vaccinations previously received.\(^13\) The case fatality rate of respiratory diphtheria is 5–10% with treatment.\(^14\) The risk of developing cardiac toxicity is correlated with the extent and severity of the bull neck and pseudomembrane coverage of the tonsils.\(^15\) Diphtheric myocarditis occurs in as many as two thirds of patients, typically 1–2 weeks after the onset of respiratory symptoms,\(^8\) and the presence of associated electrocardiographic changes predicts a three- to fourfold higher mortality rate.\(^2\) Cardiac toxicity may cause conduction disturbance, arrhythmias, congestive heart failure and circulatory collapse, and is a major cause of mortality in patients with diphtheria.\(^2,8,15\)

Neurological toxicity is also correlated with the extent and severity of the primary respiratory infection.\(^2\) Kadirova and colleagues estimate that neurological toxicity occurs in approximately 5% of patients with diphtheria.\(^16\) However, 75% of patients with severe disease will develop some form of neuropathy.\(^12\) Neuropathy may involve the soft palate, posterior pharyngeal wall and cranial nerves, leading to regurgitation or aspiration and oculomotor and ciliary paralysis.\(^7,14\) A toxic myelopathy
with paranodal demyelination can involve motor and/or sensory nerves of the trunk, neck and upper limbs. Endocarditis, myocytic aneurysms and septic arthritis have all been reported as complications of infection with non-toxigenic *C. diphtheriae* strains.17

The importance of subgroups at higher risk for invasive infection with non-toxigenic diphtheria has been described in lower socioeconomic groups associated with poor hygiene and crowding.11,18 In 1994, in both New South Wales and eastern Victoria, a cluster of cases of non-toxigenic strains of *C. diphtheriae* biovar gravis was isolated from throat swabs and skin ulcers in Aboriginal Australians.3 Endocarditis is a reported complication of infection with non-toxigenic strains in Aboriginal Australians, and this condition has a high incidence of complications and mortality.19

The cornerstone of therapy for diphtheria is diphtheria antitoxin, hyperimmune antiserum produced in horses, which neutralises the toxin produced by *C. diphtheriae*. Early treatment is critical as the degree of protection is inversely proportional to the duration of the illness before its administration.20 Hypersensitivity reactions to antitoxin may occur, so a test dose should always be given even in emergency situations. Access to diphtheria antitoxin in Australia may be limited due to cessation of production.21 Antibiotics, specifically penicillin or erythromycin, are usually administered; however, there has been little change in mortality since the availability of antibiotics.20,22 Appropriate supportive care involves maintaining an adequate airway and cardiac monitoring.20 Patients should be maintained in strict isolation during and after therapy, and until they have two consecutive negative cultures at 24-h intervals.20

Prior to the introduction of the diphtheria vaccination, clinical diphtheria was a major cause of morbidity and mortality globally. However, the introduction of routine childhood vaccination during the 1930s and 1940s has almost eliminated diphtheria in most developed countries.4 Importantly, widespread immunisation against diphtheria is the only effective method of preventing the disease.24 The World Health Organisation recommends a three-dose primary course in the first 6 months of life, followed by a booster at 1–6 years.25 In Australia, primary vaccination is achieved by vaccination of diphtheria toxoid, given together with tetanus and acellular pertussis-containing vaccines (DTPa) at 2, 4 and 6 months of age.24 In addition, a booster dose is given at 4 years of age.24 A second booster, which contains significantly less diphtheria toxoid but is essential for maintaining immunity, is recommended at 12–17 years of age.24 This adolescent/adult formulation is usually given to year 10 students as part of the school-based vaccination programme in Victoria.25 Thus, students who do not complete year 10 may develop inadequate immunity to diphtheria. Quinn and McIntyre estimate that only 65% of high school students in Australia received the tetanus, diphtheria and acellular pertussis (DTPa) vaccine in school-based immunisation programmes between 2004 and 2009.23 Further, Quinn and McIntyre suggest that implementing a broadly based vaccination programme is more beneficial than introducing the vaccine in a single school year.23 In addition, adults over 50 years should receive a booster dose of diphtheria and tetanus vaccine or diphtheria–tetanus–pertussis vaccine unless a booster dose has been documented in the previous 10 years.24 The vaccine effectiveness is 97% for the primary vaccination series,22 and immunisation results in reduced carriage of toxigenic strains of *C. diphtheriae*.2o Booster doses are, however, required to maintain immunity.

A national serosurvey performed in 200527 demonstrated that approximately 99% of Australian children at the ages of 5–9 years had diphtheria antitoxin levels ≥0.01 IU/mL, indicating immunity or partial immunity. Childhood immunity is a significant determinant of outbreak potential;24 thus, maintenance of high childhood immunisation rates is an effective means of prevention. Furthermore, antitoxin levels decline with age, and in subjects at the age of over 50 years, less than 60% were found to have immunity or partial immunity to diphtheria.23 Thus, fewer than 75% (the proportion required for herd immunity) of Australian adults over 50 years are adequately immune to diphtheria. This large and growing immunity gap, which exists within the adult population, contributes to the potential for an extensive epidemic.28 Kilham and Benn believe that many Australian adults, whose only protection from diphtheria is from childhood immunisation, are susceptible to infection due to the lack of booster vaccination.30 Therefore, additional public health measures, such as booster doses and confirming immunisation status prior to travel, are required to protect those 50 years and older.27 In addition, as immunised individuals show reduced carriage of toxigenic strains of *C. diphtheriae*, an immunity gap in Australia could result in an increase in carriage of toxigenic strains.26

Diphtheria was once a major cause of morbidity and mortality in Australia.30 Nationwide immunisation, which became widespread by the 1940s, resulted in the almost complete eradication of the disease by the 1960s.30 Sporadic cases have continued to occur in unimmunised Australians.30 The National Notifiable Disease Surveillance System reported two cases of diphtheria in 1991, four in 1992 and one in 2001.31 No further cases were reported until 10 years later; in the year 2011, four cases of diphtheria were reported.31 Kilham and Benn state that it is important to acknowledge the possibility of
resurgence of diphtheria in Australia due to the inadequate immunity in the adult population.30

Diphtheria is endemic in many developing countries, many of which are in close proximity to Australia. These countries include Papua New Guinea, Cambodia, China, India, Indonesia, Laos, Mongolia, Burma, Nepal, Pakistan, Philippines, Thailand and Vietnam.32 Furthermore, diphtheria is endemic in parts of the Middle East and Sudan,4 and re-emerged in the former Soviet States due to the disruption in public health infrastructure in the 1990s, causing more than 140 000 cases and over 4000 deaths.33 Australians who travel to endemic areas need to be fully immunised to decrease the risk of reintroducing diphtheria into Australia.27 In addition, unvaccinated or inadequately vaccinated Australians who have subsequent contact with those travellers are at risk of acquiring the infection.32 Furthermore, we hypothesise that non-immune adults (who had originally been immigrants) residing in Australia who visit friends and relatives in diphtheria-endemic countries may be a subpopulation that is at risk of both acquiring and transmitting diphtheria. It is known that this group of immigrant friends and relatives has incomplete childhood vaccinations, rarely seek pre-travel medical advice and are at increased risk of travel-related health problems.34,35

Diphtheria is a vaccine-preventable infectious disease and was the most common infectious cause of death in Australia during the pre-vaccination era.34 Routine childhood vaccination virtually eliminated diphtheria in most industrialised countries.4 In Australia, childhood immunisation rates are high; however, a large gap in adequate immunity potentially exists among early school leavers and among adults at the age of 50 years and over.27 In order to prevent the re-emergence of diphtheria in Australia, public health measures are required to increase immunity through a booster dose in adolescence and among the adult population, and to ensure that travellers to endemic regions are fully immunised. The re-emergence of diphtheria in the new independent states of the former Soviet Union in the 1990s serves as a salient reminder of the importance of adequate immunisation practices and highlights how swiftly progress in public health can be reversed. Moreover, a recent fatal case of diphtheria in Brisbane and recent positive cultures in regional Victoria highlight the need for heightened awareness and sustained vigilance of C. diphtheriae as a previously eradicated infectious disease that can have fatal consequences.

Galazka and colleagues maintain that controlling diphtheria outbreaks, high immunisation coverage, prompt diagnosis, and management and rapid identification of close contacts is paramount.7 Currently, in Australia, the diagnosis of diphtheria is difficult as most doctors are unfamiliar with its clinical presentation. Physician unfamiliarity and the potential for mild clinical cases as a result of partial immunity creates a lack of recognition of diphtheria in clinical practice, and delayed diagnosis increases the risk of transmission to susceptible individuals. Health policy-makers and clinicians alike should not underestimate the importance of primary vaccination and booster vaccinations against diphtheria among healthy adults and travellers.

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References


Marantic endocarditis presenting with multifocal neurological symptoms


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Key words
endocarditis, non-infective, neoplasm, stroke, echocardiography, neuroimaging.

Abstract
Non-bacterial thrombotic endocarditis (NBTE), also known as marantic endocarditis, has been reported to occur in 0.3–9.3% of the adult population at autopsy. NBTE associated with malignancy is an underrecognised cause of thromboembolic disorders. The clinical spectrum encountered and investigation results can be non-specific, often mimicking other acute conditions such as infective endocarditis. We describe the case of a 34-year-old woman with non-localising and multifocal neurological symptoms, who was subsequently diagnosed with NBTE secondary to a resectable primary lung adenocarcinoma.

A 34-year-old female ex-smoker with a 20-pack year history presented with a 3-week history of intermittent headaches, decreased vision, left-sided clumsiness, as well as non-specific left neck, thoracic and arm pain. Her only medication was the oral contraceptive pill. Physical examination revealed decreased sensation along the left-sided C5-T1 dermatomes with impaired coordination of the left upper and lower limbs. Assessment of cranial nerves revealed bilateral reduced visual acuity without corrective aids of 6/18 of the left eye and 6/38 of the right eye secondary to her chronic myopia.

Computed tomography of the brain and cervical spine revealed a disc protrusion at C3/4. A subsequent magnetic resonance imaging (MRI) of the brain revealed multiple bilateral cerebral and cerebellar foci of T2/FLAIR hyperintensity, with the involvement of multiple vascular territories suggestive of an embolic source (Fig. 1A–C). Further imaging demonstrated a F-18 fluorodeoxyglucose avid left hilar mass and an asymptomatic splenic infarct (Fig. 1D). Laboratory investigations including thrombophilic, vasculitic and infective screens were largely negative apart from a non-specific rise in antinuclear antibody speckled titre >640. Cerebrospinal fluid analyses and carotid Doppler ultrasounds were unremarkable. Transthoracic echocardiography (TTE) revealed a mildly thickened aortic valve with a small strand (Fig. 2A). The subsequent trans-oesophageal echocardiography (TOE) confirmed a mass attached to the ventricular aspect of the right coronary cusp of the aortic valve (Fig. 2B). At this stage, she was anticoagulated with aspirin and warfarin.

An endobronchial ultrasound and biopsy of the left hilar mass was diagnostic of large cell carcinoma not otherwise specified. She was thus staged as T2aN0M0 and proceeded to a left upper lobectomy that identified a well-differentiated adenocarcinoma in the lingular segment with a hilar nodal mass and microscopic involvement of the ipsilateral mediastinal lymph nodes on final pathology (T1aN2M0). Five weeks postoperatively, she received adjuvant chemotherapy with a platinum and vinorelbine regimen followed by consolidative radiotherapy to the mediastinum of 50 Gray in 10 fractions. Her warfarin had been switched to enoxaparin for the duration of treatment. At completion of
chemotherapy, a repeat TOE demonstrated resolution of the aortic valvular lesions (Fig. 2C). The enoxaparin was ceased, and no further anticoagulation was prescribed. To date, 13 months postoperatively, she remains well with no evidence of recurrence and stable neurology.

The incidence of NBTE has been variably reported from 0.3% to 9.3% of the general population. One of the larger autopsy series conducted more than 30 years ago found 65 cases of NBTE among about 4000 patients, correlating to an incidence of 1.6% in the adult population, although 78% of these cases were associated with a malignant process. This is comparable with a prospective echocardiographic study where NBTE had an incidence of 19% in patients with solid malignancies compared with 2% in the control group without overt heart disease who were referred for TOE. In contrast, an autopsy series of 1640 patients performed in the 1990s indicated an incidence of NBTE of 1.25% in patients with malignancy versus 0.2% in those without cancer. Hence, there are large variations in the literature in terms of the incidence and prevalence of NBTE.
NBTE may complicate rheumatic and autoimmune conditions, hypercoagulable states, sepsis, indwelling catheters and acquired immune deficiency syndrome. In malignancy, it is most commonly associated with mucin-producing adenocarcinomas as occurs in gastrointestinal, lung and prostate malignancies. NBTE is characterised by the presence of aseptic vegetations on previously undamaged cardiac valves. These consist of fibrin and platelet aggregates and are devoid of inflammation. The vegetations may vary in size, are often friable, and are usually located on the mitral and/or aortic valves. Involvement of the right-sided valves, although uncommon, has been reported. It can be difficult to differentiate valvular masses on echocardiography where aetiologies range from infective endocarditis, tumours such as benign cardiac papillary fibroelastomas and Lamb’s excrescences, wear-and-tear lesions that originate in the endothelium of the contact margins of a valve. All of these pathologies can cause systemic embolisation and hinder a clinical diagnosis of NBTE.

The exact pathogenesis of NBTE remains unclear. In malignancy, several mechanisms have been postulated. First, some cancers are capable of directly activating the clotting cascade leading to the generation of thrombin and thrombosis. Second, malignant cells can interact with cells of monocyte or macrophage lineage, inducing a host response that includes production of tumour necrosis factor, interleukin-1 and interleukin-6. These cytokines and the resulting inflammatory response may cause endothelial damage and propagate clot formation. In the setting of shear forces from turbulent blood flow or structurally deficient valves, cardiac valves are particularly susceptible to the formation of vegetations.

There are neither pathognomonic signs nor symptoms of NBTE. Cardiac murmurs are frequently absent and small vegetations commonly embolise, leaving only tiny remnants on the valves. In a retrospective study of 51 patients with cerebrovascular accidents and active malignancy, nine were diagnosed with NBTE on TOE. Seven patients had a previous TTE, and NBTE had been missed in 57% of cases. Therefore, TOE has higher sensitivity for the detection of small vegetations, although it is more invasive than TTE. Cardiac MRI has not yet been validated for the detection of NBTE but has demonstrated vegetations in case reports.

The clinical manifestations of NBTE result from systemic embolisation in up to 50% of patients rather than valvular dysfunction. The most frequently affected organs include the spleen, kidney, brain and heart with potentially life-threatening consequences. It has been suggested that NBTE is associated with a higher incidence of stroke (33%) as compared with infective endocarditis (19%). Part of the difficulty in making a diagnosis of NBTE is that its presentation can mimic other conditions such as leptomeningeal metastases and infective endocarditis. Diffusion-weighted MRI can potentially demonstrate differences between cardio-embolic strokes from infective endocarditis and NBTE. In a retrospective study, patients with NBTE were reported to have multiple, disseminated lesions, while patients with infective endocarditis presented with a variety of stroke patterns. This was presumed to be secondary to the lack of cellular organisation and higher fragmentation potential in the vegetations found with NBTE. Surprisingly, the size of the vegetations did not correlate with the size, number or pattern of strokes.

Because of the limited number of documented NBTE cases and the often palliative intent once NBTE has developed, there are no consensus guidelines for its management. Treatment of the underlying condition is the best method of preventing recurrent embolism. Systemic anticoagulation with heparin is often used despite a lack of prospective randomised evidence to support this strategy. Oral anticoagulation is a less attractive option, as it has been shown to be inferior to heparin in preventing recurrent thromboembolism in the context of malignancy. It is unknown whether anticoagulation has any effect on mortality. There are isolated cases of successful prevention of recurrent embolism and resolution of NBTE with anticoagulation, but whether this applies to cases with large, mobile vegetations is unclear. Anticoagulation should be continued indefinitely in patients with advanced disease, especially where there has been either resolution or improvement of symptoms. In patients with extensive cerebral infarction, anticoagulation should be carefully considered given the risk of haemorrhagic transformation.

The role of surgical intervention in NBTE remains unclear. Early diagnosis of NBTE and institution of treatment such as systemic anticoagulation could prevent the need for cardiac surgery. Surgery should be considered for patients presenting with severe valvular dysfunction, decompensated congestive cardiac failure and recurrent thromboembolism despite adequate anticoagulation. Surgical excision of the vegetations with or without valve replacement has proven effective in highly selected cases. However, most patients with NBTE have advanced disease and therefore limited life expectancy on presentation. In these cases, surgery is most often inappropriate in view of its attendant morbidity.

The presented case illustrates the importance of NBTE as a consideration in the diagnostic work-up of patients with systemic embolisation. It should be suspected in culture-negative endocarditis. The recognition of a more disseminated stroke pattern on diffusion-weighted MRI may assist in distinguishing between NBTE and infective
endocarditis. If suspicious of NBTE, TOE is mandated as TTE has been shown to lack sensitivity. Although most patients with NBTE have poor clinical outcomes, our case highlights the possibility of resolution of the valvular lesions through anticoagulation and management of the primary malignancy.

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Androgenic-anabolic steroid drug-induced liver injury

Bodybuilders and athletes frequently abuse androgenic-anabolic steroids (AAS), which have both physiological and metabolic consequences. The prevalence of AAS abuse is increasing, with reported rates of 15–30% in weight trainers in health clubs and gyms. AAS are increasingly being used for their cosmetic benefit, with the number of reported steroid users increasing in the high school population group; approximately 6.6% of year 12 students in America were reported to have taken AAS in 1988. More recent reports estimate rates of 3–12% of male and 0.5–2% of female adolescents. Similar figures have been reported in several countries in Europe, and in Australia and Brazil, with a lifetime prevalence of AAS use between 1% and 6% for high school students, and between 9% and 38% among bodybuilders. This trend has not only resulted in an increase in anabolic-steroid-associated reproductive and endocrine disorders, myocardial hypertrophy, stroke, aggression, and depression, but has also been associated with hepatocellular injury. Due to the illicit nature of AAS and the relative paucity of reported cases, there is little consensus on diagnosis, monitoring or therapy for AAS-induced hepatocellular injury.

We report the case of a 46-year-old man who presented to the emergency department with a 3-month history of painless jaundice and weight loss of 9 kg over 3 weeks. He had ceased his AAS use 5 months prior to presentation. He reported nausea, pruritus and anorexia. He had ingested stanozolol (40 mg) and methandrostenolone (40 mg) daily for 2 months, and reported stopping usage 5 months prior to his initial symptoms. There was no other exposure to drugs associated with cholestatic liver injury. There was no history of significant alcohol intake, intravenous drug use or herbal medication intake, and his body mass index was 28.5. Examination revealed jaundice, icterus and a mildly tender right-upper quadrant. There was no encephalopathy, and he was haemodynamically stable. Liver function tests showed a mixed cholestatic and hepatitic pattern, with alkaline phosphatase 295 U/L, gamma glutamyl transpeptidase 114 UL, alanine transaminase 125 U/L and bilirubin of 302 μmol/L (conjugated bilirubin of 127 μmol/L). There was no synthetic dysfunction. Viral and autoimmune serologies were unremarkable. Ultrasound of the liver and computed tomography of the abdomen were normal. A liver biopsy showed intrahepatic cholestasis and occasional necroinflammatory foci, consistent with a drug reaction and proliferation (indicative of stanozolol usage) (Fig. 1). He was commenced on ursodeoxycholic acid treatment, and at week 7 post-discharge, he had complete resolution of his jaundice, and liver function tests and ursodeoxycholic acid was ceased.

In the setting of controlled medical use, AAS are rarely associated with jaundice. Abuse of AAS is becoming an increasingly common problem; four out of every five users of AAS have been found to be non-athletes, taking these drugs for cosmetic reasons, with most taking larger doses than previously recorded.

17α-AAS include the compounds methyltestosterone, methandrostenolone, oxymetholone, oxandrolone and stanozolol. Long-term AAS use has been linked to a spectrum of liver injury, such as peliosis, adenoma and hepatocellular carcinoma. Stanozolol is a 17α-AAS that is often misused by athletes and bodybuilders. Drug-induced liver injury secondary to AAS usually presents with painless jaundice. The level of jaundice appears to be dose-dependent. The pattern of liver function derangement most often described in association with AAS is a mixed cholestatic and hepatitic picture, which corresponds with the intrahepatic cholestasis and hepatocellular necrosis found in liver biopsy.

AAS have been shown in adult male rats to result in moderate inflammatory or degenerative lesions in
hepatocytes, and alters the liver’s ability to metabolise xenobiotics. It is postulated that high doses of stanozolol may cause proliferation of hepatocytes, which was demonstrated in our patient’s liver biopsy. The drug-induced liver injury caused by AAS is thought to be due to direct hepatotoxicity of the AAS, which appears to be dependent on individual susceptibility. The drug-induced cholestasis appears to be reversible upon withdrawal of AAS. Supportive care with reversal of coagulopathy and empirical usage of ursodeoxycholic acid has shown improvement of hepatic dysfunction.

The case presented here differs from those previously reported in that the obstructive jaundice developed only 5 months after commencing AAS, whereas most cases have been described at the time of commencement or within weeks of usage. Recovery was prolonged, requiring 5 months of abstinence from stanozolol use.

Common drugs causing cholestasis or cholestatic hepatitis, such as clavulanic acid, flucloxacillin and terbinafine, need to be considered initially. However, it is important to consider abuse of AAS in cases where the diagnosis is proving difficult, particularly in certain demographics such as young age. Our case also demonstrates that the utility of a liver biopsy as findings suggestive of hepatotoxicity secondary to cholestasis may aid in the diagnosis of patients.

AAS-induced hepatocellular damage can be a challenging diagnosis for clinicians, largely due to its covert usage. A high index of suspicion is required to make the diagnosis, and counselling regarding abstinence from ongoing use is required to prevent progressive drug-induced liver disease.

Thrombotic thrombocytopenic purpura associated with adalimumab (Humira) treatment in Crohn disease

This is a case of a patient who developed thrombotic thrombocytopenic purpura (TTP) during her treatment with adalimumab (Humira) for Crohn disease. There is no prior documentation of such cases. However, there are rare reports of cytopenias with adalimumab.

A 44-year-old woman who presented with a 4-day history of nausea and bile-stained vomiting after her fourth dose of fortnightly adalimumab for Crohn disease.
There were no fevers, melaena, haematemesis, haematuria, visual disturbance or weakness. The patient developed a small amount of bloody diarrhoea, a continuous frontal headache over the past 24 h and had been anuric for 6 h. Examination was unremarkable apart from the presence of purpura on both arms. Her blood tests showed a haemoglobin (Hb) of 77 g/L, reticulocyte count of 1.7% and platelets of 65 \times 10^9/L. Her creatinine was 171 \mu mol/L, urea 16.6 mmol/L, with an estimated glomerular filtration rate of 28, conjugated bilirubin of 11 \mu mol/L and total bilirubin of 56 \mu mol/L. The lactate dehydrogenase (LDH) was 618 units/L and haptoglobins was <0.1 g/L, with a normal prothrombin time, activated partial thromboplastin time and fibrinogen. The patient’s blood film showed schistocytes and fragmentation haemolysis.

This was a clinical picture consistent with TTP, with a microangiopathic haemolytic anaemia, acute renal failure, thrombotic purpura on the arms and headache as a neurological abnormality. Acute management involved transfusion of 28 units of fresh frozen plasma and 6 units packed red blood cells with subsequent plasmapheresis. Mrs DB improved clinically and biochemically over 10 days, with the following results: Hb 90 g/L, platelet 409 \times 10^9/L, creatinine 64 \mu mol/L and LDH 205 units/L.

This patient has a background of extensive small bowel (jejunal) Crohn disease, which was diagnosed in 2010 on computed tomography enterography, with granulomas found on biopsies taken from a macroscopically normal colon. She was started on adalimumab after her disease was unresponsive to azathioprine and prednisone.

Adalimumab is a currently accepted treatment in Australia for more severe forms of Crohn disease. Increasingly, there have been calls to introduce treatment with anti-tumour necrosis factor (TNF) agents during the early stage of the disease. However, anti-TNF agents have a variety of side-effects, including infections, cardiovascular disease, demyelinating disease, lupus-like disease, lymphoma, skin and allergic reactions, and less commonly systemic complications such as pancytopenia and aplastic anaemia. To our knowledge, there has been no previous case report that has documented the occurrence of TTP as a result of adalimumab therapy. There have been three cases of thromboembolic events during adalimumab treatment and rare reports of medically significant cytopenias with adalimumab, such as thrombocytopenia and leukopenia.

There have also been rare reports of an association between TTP and inflammatory bowel disease (IBD). However, it is unclear whether IBD causes or predisposes to TTP. In this case, TTP being precipitated by adalimumab therapy is evidenced by the overwhelming time relationship and the extensive investigations to rule out other precipitants.

Anti-TNF therapy is associated with induction of autoantibodies, in particular antinuclear antibodies, with rare occurrence of a lupus-like syndrome. A possible explanation for the occurrence of TTP in this patient is through induction of autoantibodies against ADAMTS13, which is a metalloprotease that cleaves von Willebrand factor multimers. ADAMTS13 activity is almost universally low in patients suffering from TTP and is commonly associated with antibodies to ADAMTS13.

More recently, it has been mentioned that ADAMTS13 levels are lower in IBD, and this may have predisposed our patient to TTP when commenced on adalimumab. Unfortunately, ADAMTS13 activity was not measured in this patient. Further research is needed to establish the frequency and mechanism of TTP as a side-effect of adalimumab.

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References
General correspondence

Why older patients of lower clinical urgency choose to attend the Emergency Department

We submit comments on the paper by Lowthian et al.\(^1\). Their study is welcomed because the question of why people choose Emergency Department services over general practitioner (GP) services for low-urgency medical care has long been overlooked. Our comments relate to the nexus between service choice, and patient and clinician attitudes that we believe is an area deserving of more detailed investigation.

The findings that patients living alone reported higher levels of social support contrast with our work on a younger cohort of patients with chronic disease frequently readmitted after presentation to emergency. We found no correlation between levels of support and frequent emergency department use.\(^2\)

Lowthian et al.\(^1\) reported on the lack of assertiveness contributing to reduced access to GP services, suggesting that this cohort represents a group who are marginalised in general practice because of lack of assertiveness in seeking care. We also found evidence of this in clinician attitudes to frequently readmitted patients.\(^3\) Conceptually, access should include the complex and subtle interplay between patient skills and attitudes, and service-related factors, such as clinician attitudes, which influence patient choice.\(^4,5\)

The reported undertriaging of patient urgency raises the question of clinician attitudes to frequent users who might be seen as being to blame for emergency overcrowding.

The authors observed that collecting data by interview avoided the problem of poorer responses from people with lower literacy skills. The exclusion of people with lower literacy from research about service use and choice means that their experiences and reasons for service choice are not translated into service design. The impact of exclusion is that services may be even less accessible to this group.

Emergency Department service preference is influenced by lack of assertive care-seeking skills in patients and the attitudes of care providers. Further exploration of these factors is a fruitful area of research.

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References


Reply

We thank Kirby et al.\(^1\) for their remarks about our study.\(^2\) Their comments further highlight the complex issues involved when patients attend a hospital emergency department instead of a clinically appropriate alternative, such as their general practitioner (GP). It is not clear to us, however, that the cohort in our study is . . .
marginalised in general practice because of lack of assertiveness in seeking care. The reasons we identified primarily related to health professional or bystander referral, patient/family dissatisfaction with GP or specialist appointment waiting times, and patient/family preferences for hospital-based care.

We do agree that this is an important topic that requires further research to help inform strategies to deal with the growing demand by the elderly for hospital emergency care.1

References


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