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EDITORIAL

What we know and do not know about women and kidney diseases: questions unanswered and answers unquestioned: reflection on World Kidney Day and International Women’s Day

Introduction

Chronic kidney disease (CKD) affects approximately 10% of the world’s adult population: it is within the top 20 causes of death worldwide, and its impact on patients and their families can be devastating. World Kidney Day and International Women’s Day in 2018 coincide, thus offering an opportunity to reflect on the importance of women’s health and specifically their kidney health, on the community, and the next generations; as well as to strive to be more curious about the unique aspects of kidney disease in women, so that we may apply those learnings more broadly.

Girls and women, who make up approximately 50% of the world’s population, are important contributors to the society and their families. Besides childbearing, women are essential in childcare and contribute to sustaining family and community health. Women in the 21st century continue to strive for equality in business, commerce and professional endeavours, while recognising that in many situations, equality does not exist. In various locations around the world, access to education and medical care is not equitable among men and women; women remain under-represented in many clinical research studies, thus limiting the evidence base on which to make recommendations to ensure best outcomes (Fig. 1).

In this editorial, we focus on what we know and do not know about women’s kidney health and kidney disease, and what we might learn in the future to improve outcomes for all.

What we know and do not know

Pregnancy is a unique challenge and is a major cause of acute kidney injury (AKI) in women of childbearing age; AKI and pre-eclampsia (PE) may lead to subsequent CKD, but the entity of the risk is not completely known. CKD has a negative effect on pregnancy even at very early stages. The risks increase with CKD progression thus posing potentially challenging ethical issues around conception and maintaining pregnancies. We do know that PE increases the probability of hypertension and CKD in later years, but we have not evaluated a surveillance or renoprotective strategy to determine if progressive loss of kidney function can be attenuated.

Specific systemic conditions, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic scleroderma (SS), are more likely to affect women than men. We do not know the relative contribution of these acute and chronic conditions on progression to end-stage renal disease (ESRD) in women.

In CKD cohorts, the prevalence in women is always less than in men, and they have slower progression to ESRD. We do not know why and how much of this is due to differences in identification of kidney impairment, different access to care, or true difference in disease severity and prevalence.

Women with CKD have a higher cardiovascular risk than women without CKD; their risk is still lower than that of men with similar degrees of kidney impairment. In haemodialysis cohorts, there are differences in vascular access types in women versus men, which may be due to biological or systemic factors. In some locations, there is differential use of peritoneal and haemodialysis in women and men.

Women are more likely to donate kidneys for transplantation than to receive them. We do not know if this is because of the differential incidence of CKD in men versus women, cultural factors or other reasons.

There remain gender differences in access to care in different regions of the world, and we do not have data to evaluate directly the extent of these differences, in the poorest parts of the world in particular.
Pregnancy, PE, pregnancy-induced hypertensive disorders and foetal health: the importance of women’s health and kidney health of present and future generations

What we know

PE is the principal cause of AKI and maternal death, particularly in developing countries. Pregnancy is the most common cause of AKI in women of childbearing age. Several diseases and conditions, besides PE, hypertensive disorders of pregnancy and CKD, can lead to pregnancy-related AKI. Causes vary in different regions. Septic abortion after an illegal procedure is the leading cause of early AKI in countries where legal abortions are not available, while PE after assisted fertilisation is becoming a leading cause in developed countries.

PE and hypertensive disorders of pregnancy occur in 3–10% of all pregnancies; in these disorders, the kidney is the main target of an unbalanced pro-angiogenic and anti-angiogenic derangement, leading to hypertension, proteinuria and widespread endothelial damage. The incidence of PE, higher in low-middle income countries (possibly reflecting undiagnosed predisposing diseases), peaks at the extremes of reproductive age for reasons mentioned above.

The relationship between kidney and placenta is bivocal, and the presence of CKD is a risk factor for PE and hypertensive disorders of pregnancy (Fig. 2). Besides CKD, other conditions cited as risk factors for PE (diabetes, immunologic diseases, baseline hypertension, obesity and metabolic syndrome) are also risk factors for CKD. Given that even minor alterations of kidney function are present in many of these disorders, the importance of kidney function is indirectly recognised in the development of PE. Newer definitions of PE recognise differences between ‘placental’ and ‘maternal’ causes of PE, based on novel angiogenic-antiangiogenic markers, which may be important for management during and after pregnancy.

There are long-term effects of PE on both maternal and foetal health, but this remains an area of active research with many unknowns.

PE is a risk factor for the future development of CKD and ESRD in the mother. The reasons are not fully understood; podocyte loss is a hallmark of PE, suggesting permanent glomerular damage. Endotheliosis, associated with PE, but also found in normal pregnancies, may herald glomerulosclerosis; tubular and vascular damage may co-exist.

Besides maternal risks, PE is associated with intrauterine and perinatal death, preterm delivery and restricted intrauterine growth; the latter two are linked to ‘small
babies. Small babies and preterm babies have highly increased risks of neurological deficits and postnatal complications, especially sepsis. The risks may be higher in low-income countries, since survival and deficit-free survival depend on the provision of postnatal intensive care. In the long term, small babies are at risk for the development of diabetes, metabolic syndrome, cardiovascular diseases (CVD) and CKD in adulthood. Since kidney development is completed in the last phases of pregnancy, delayed, insufficient kidney growth, resulting in low nephron number is probably the basis of the increased risk of CKD and hypertension in small for gestational age and preterm babies.

Pregnancy in CKD, dialysis and transplantation

What we know

Chronic kidney disease

CKD is a risk factor for adverse pregnancy outcomes from its early stages (Table S1, Supporting information). The risks increase from CKD stage 1 to CKD stage 5, and may be higher in glomerular nephropathies, autoimmune diseases and diabetic nephropathy. Results of pregnancy after kidney donation suggest that reduction of kidney parenchyma may be associated with a higher risk of PE and hypertensive disorders of pregnancy.

Hypertension and proteinuria at baseline are important modulators of pregnancy-related risks; among the risks, we know that malformations are not increased with respect to the overall population (out of the context of inherited diseases, such as reflux nephropathy, polycystic kidney disease or congenital anomalies of the kidney and urinary tract), maternal death is unusual (in highly resourced countries), while the incidence of preterm delivery and of small for gestational age babies, intrinsically linked, is increased in stage 1 CKD patients and rises with the worsening of kidney function. Similarly, the effect of pregnancy on CKD progression is not fully understood because of different study designs, obstetric policies and duration of follow-up. Overall, short- and long-term decrease in kidney function is unusual in early CKD, but the risk increases as CKD severity increases.

Pregnancy is a potential occasion for the initial diagnosis of CKD. In poorly or unevenly resourced countries, advanced CKD may be discovered only during pregnancy. The implications of dialysis initiation may present important clinical and ethical issues; in highly resourced countries with established prenatal care, the diagnosis of earlier stages of CKD may lead to more intensive therapy and surveillance.

Dialysis and transplantation

Fertility is reduced in ESRD; Australian and European data suggest a 1:10 ratio from general population to transplantation and from transplantation to dialysis (1:100 probability as compared to the general population). The first sporadic cases of successful pregnancy

Figure 2 Pregnancy and kidney function: complex interactions between two organs, the kidney and placenta. AKI, acute kidney injury; CKD, chronic kidney disease; PE, pre-eclampsia.
on dialysis were described in the 1970s, but in the new millennium this became an acknowledged real clinical possibility.8,54,55

More than 1000 pregnancies have been reported in dialysis patients.39 The most important advance has been the demonstration of a strong relationship between the intensity (frequency and duration) of the dialysis sessions and positive pregnancy results: thus, intensifying dialysis up to daily, is the current standard of care.6,54 Changing attitudes towards counselling women with advanced CKD may be impacted, with the knowledge of positive outcomes on dialysis for women and their offspring.

Fertility is partly restored after kidney transplantation.56–60 However, even in an ideal situation (normal kidney function, no hypertension or proteinuria, at least 2 years after transplantation, without recent rejection episodes), the risk of complications is higher in women with transplanted kidneys than in the general population. However, if teratogen drugs are avoided (mycophenolic acid and rapamycin), the outcomes of pregnancy after kidney transplantation share the same risk factors as CKD (kidney function, hypertension and proteinuria).59

Experience with pregnancy in patients with a reduced renal function or failing kidney graft is limited and counselling is still forcibly based on personal experience or indirect evidence.61,62 Assisted fertilisation techniques are increasingly popular in some settings, but dedicated studies in CKD patients are few; multiple pregnancies may bear an added risk in CKD patients, with both native and transplanted kidneys.

**Autoimmune diseases, women and kidney disease**

**What we know**

Autoimmune diseases, such as SLE, RA and SS, preferentially affect women and are characterised by systemic inflammation leading to target organ dysfunction, including the kidneys. Sex differences in the incidence and severity of these diseases result from a complex interaction of hormonal, genetic and epigenetic factors (Table 1). The public health burden of autoimmune diseases, which collectively represent a leading cause of morbidity and mortality among women throughout adulthood, is substantial.63–65

SLE is an autoimmune disease with multiple organ involvement, affecting approximately five million people worldwide; disproportionately predominant in women (9:1 female-to-male ratio) and individuals of non-European ancestry. The highest female predominance (up to 15:1) is in peak reproductive years. The biology of these differences has been explored: one explanation is the number of X chromosomes and genetic variants on the X chromosome.66–68 Another important aetiological explanation is the role of oestrogen in SLE. Oestrogen’s primary effects are mediated by transcription activity of the intracellular oestrogen receptors, whose profile is altered in T-cells from female SLE patients.69,70 Cathepsin S protein has recently been identified as a potential cause of lupus, triggering the immune system to attack healthy cells, particularly in females.71 Numerous non-human leukocyte antigen genetic markers may predispose individuals of European, Hispanic and Afro-American ancestry to lupus.72 Susceptibility to SLE during pregnancy is also multifactorial; one factor being upregulation of IFN-α. Elevated IFN-α, expressed by the placenta, plays a pathogenic role in SLE, contributing both to the success of placental reproduction and to increased susceptibility to SLE.73 Regulatory T-cells (which may be the key to cell modulating foeto-maternal tolerance) have abnormalities of structure and function, and may contribute to pregnancy pathology in women with SLE and to challenges of managing them during pregnancy.74 SLE affects kidneys in about 50% of patients, including glomerular, interstitial and vascular lesions. Lupus nephritis is a major risk factor for overall morbidity and mortality in SLE, and despite potent therapies still leads to significant impairment of kidney function for many patients.75 Kidney disease is a critical concern in counselling women with lupus considering pregnancy, with previous kidney involvement and lower C4 levels conferring high risk of active nephritis occurring in pregnancy.76 Socioeconomic disparities are also linked to the health of

**Table 1 Sex differences in the incidence and severity of autoimmune diseases**

<table>
<thead>
<tr>
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<th>SLE</th>
<th>RA</th>
<th>SS</th>
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<tbody>
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<td><strong>Peak incidence</strong></td>
<td>Reproductive age</td>
<td>Perimenopausal</td>
<td>After 50–60 years</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>Peak: 15:1</td>
<td>Peak: 4:1</td>
<td>Peak: 14:1</td>
</tr>
<tr>
<td></td>
<td>Total: 9:1</td>
<td>After 60 years: 1:1</td>
<td>Total: 3:1</td>
</tr>
<tr>
<td><strong>Influence of oestrogen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High levels</td>
<td>Negative</td>
<td>Positive</td>
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<tr>
<td>Low levels</td>
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RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, systemic scleroderma.
patients with lupus. Poverty is associated with an increased long-term level of accumulated disease-associated damage and a 1.67 times increased likelihood of experiencing a clinically meaningful increase in damage. Frequency of adverse pregnancy outcomes in women with lupus is twofold higher in black and Hispanic women than in white women. In blacks, socioeconomic status was a determinant of pregnancy outcomes and a key contributor to adverse pregnancy outcomes.\textsuperscript{77,78}

RA also preferentially affects women (4:1 ratio to men) with the peak incidence at age 45–55, coinciding with the perimenopausal years. This suggests a possible association between oestrogen deficiency and disease onset. Female-to-male incidence ratio after the age of 60 years is approximately 1:1, potentially implicating changes in sex hormones in the development of RA, and a pattern of RA symptom improvement or even remission during pregnancy is well recognised.\textsuperscript{79–81} Renal involvement in RA is relatively common and multifactorial and is a predictor of mortality in RA patients. The risk of CKD is significantly higher in patients with RA than in the general population. The development of CKD may result from several ongoing processes, including specific renal involvement associated with RA (e.g. glomerulonephritis, interstitial nephritis), chronic inflammation, comorbidities and nephrotoxic anti-rheumatic drugs. The strong association between RA activity and AA amyloidosis increases morbidity and is the main cause of ESRD with RA and nephropathy. Importantly, some of the life-long and combined RA pharmacotherapy can lead to various renal side effects.\textsuperscript{82–84}

SS predominantly affects women (female-to-male ratios ranging from 3:1 to 14:1), with the peak incidence in the fifth and sixth decades. Oestrogen may play a role in scleroderma pathogenesis through its stimulatory effect on transforming growth factor-beta 1 receptor and platelet-derived growth factor receptor.\textsuperscript{85} Vasculopathy is an important disease-related manifestation in SS, and the low oestrogenic state associated with menopause has been suggested to aggravate vascular manifestations in affected women.\textsuperscript{86} SS can also be complicated by several different forms of kidney disease, including scleroderma renal crisis, which represents a form of malignant hypertension with acute renal failure; or more commonly ischaemic nephropathy leading to slowly progressive CKD, accompanied by hypertension and albuminuria.\textsuperscript{78} Normotensive acute renal failure in patients with SS may be caused by interstitial nephritis or anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, a separate entity in scleroderma with poor outcome.\textsuperscript{87–89}

**Women, CKD and access to renal replacement therapies**

**What we know**

Although renal replacement therapy (RRT), including dialysis and transplantation is life sustaining, not all patients receive RRT. The rate of ESRD treated by RRT differs greatly between countries and regions, and intricately depends on the economy of a country and healthcare system.\textsuperscript{90,91} Worldwide, only 50% of patients requiring RRT receive treatment,\textsuperscript{92} and in low- and middle-income countries and regions, even less; in large parts of sub-Saharan Africa, less than 2% of ESRD are treated by RRT.\textsuperscript{93} The equality of access to RRT for women and girls is of particular concern because, in many societies, they are disadvantaged by discrimination rooted in sociocultural factors.\textsuperscript{94,95}

**Sex differences in access to dialysis**

At least 2.284 million people may have died prematurely due to lack of access to RRT with treatment gaps being much larger in low-income countries, with conservative estimates in Asia and Africa of 1.907 million and 432 000 people not receiving RRT. By 2030, the estimated number of RRT should be more than double to 5.439 million (3.899–7.640 million), with the most growth in Asia (0.968 million to a projected 2.162 million (1.71–3.14 million)).\textsuperscript{92} These numbers are derived from an extensive systematic review.

There are few data to compare the gender difference for the treatment gaps. Studies in Africa show that men were more likely to receive RRT than women.\textsuperscript{96,97} In Japan, the incidence of treated ESRD in females was less than half of that in males (3287 in males vs 1764 women per million population treated):\textsuperscript{91} no explanations are given for this finding. One US study reports women having significantly higher odds ratio of 1.70 for late initiation of dialysis compared to men.\textsuperscript{98} Awareness levels of previous kidney disease in women were reported much lower than in men (2.9 ± 1.6% in women vs 17.9 ± 5.9% in men), which may contribute to later initiation of RRT.\textsuperscript{99}

Mortality rates are similar in men and women on dialysis, but the incident rates of some dialysis-associated complications and morbidity are higher in women. A US report of hospitalisations in 111 653 patients undergoing maintenance haemodialysis describes higher hospitalisation rates in women and higher risk for 30-day readmissions.\textsuperscript{100}

In addition, the prevalent use of arteriovenous fistula, which is associated with reduced mortality, complication
and costs, is lower among female than male haemodialysis patients.\textsuperscript{101} This may be due to several different factors, including anatomical/surgical issues related to vessel size, timing of referral and attitudinal differences. This has not been systematically studied.

Dialysis dose which is evaluated by \( \frac{Kt}{V} \) may result in under-dialysis in women who have an average smaller volume of urea distribution or total body water than men.\textsuperscript{102} Women receiving dialysis have also been reported to have worse clinical parameters, including anaemia, nutrition and quality of life.\textsuperscript{103} Reasons are uncertain.

**Sex differences in access to kidney transplantation**

Transplantation represents the best form of RRT in patients without contraindications. Worldwide data describe that women are less likely than men to be kidney transplant patients, either from a cadaveric or living donor, but are more likely to serve as living donors for kidney transplantation.\textsuperscript{104} Data from different countries, including the United States, France, China and India, confirm differential kidney transplant rates (lower in women than men), less likelihood of women being registered on national transplant waiting lists and longer time from dialysis initiation to listing. Mothers are more likely to be donors, as are female spouses.\textsuperscript{91,105–108} Sex inequality also exists in the paediatric population. A survey from 35 countries participating in the European Society for Pediatric Nephrology/European Renal Association-European Dialysis and Transplant Association Registry, reported girls had a lower access to renal transplantation than boys.\textsuperscript{109}

Socioeconomic factors undoubtedly play a role in the inequality of transplantation between sexes, especially in the low- and middle-income countries and regions. Generally, men provide the major income for their family which may discourage them to donate kidneys. Different employment status and incomes between genders may contribute to sex differences in transplantation because employment and income status is usually associated with better healthcare insurance which cover the costs for transplantation. Psychosocial factors and education of women have been suggested as a contribution to sex disparity. US data found black women were less likely to want living donor kidney transplantation compared with men, despite being twice as likely as men to receive unsolicited offers for kidneys. They were also less likely to have been evaluated for a kidney transplant.\textsuperscript{110} Other reports describe disparities in age and sex in access to kidney transplantation which originate at the time of pre-referral discussions about kidney transplantation; irrespective of age, women were more likely not to have had discussions with medical professionals. This result may imply that there is a need for better clinical guidelines and education for women, their social network and their providers.\textsuperscript{111}

**Present and future what we do not know**

Given the data presented above with respect to pregnancy, AKI, autoimmune diseases, CKD, dialysis and transplantation, there are many unanswered questions. In high-income countries with increasing maternal age and assisted fertilisation, there may be an increase in PE which may impact future generations if associated with adverse foetal outcomes. The increase in \textit{in vitro} fertilisation techniques for those of advanced maternal age may lead to multiple pregnancies, which may predispose to PE, intrauterine growth restriction or both. Will this lead to an increase in CKD and CVD for women in the future?

Due to the high heterogeneity of CKD, we do not know if and how pregnancy outcomes are modulated by the different nephropathies, as besides the most common ones, such as IgA or lupus nephropathy, diabetic nephropathy and reflux nephropathy, evidence is scant.\textsuperscript{44,45,112–114} How should we define preconception risks of pregnancy with respect to current proteinuria cut-offs? Neither indications on when to start dialysis in pregnancy are well established nor is the specific role of frequency and duration. In those with kidney transplants, given the changing expanded donor policies, higher age at transplantation and reduced fertility in older women, there may be changes in attitudes towards pregnancy with less than optimal kidney function.\textsuperscript{56,60} How this will impact short- and long-term outcomes of mothers and their babies is not clear.

Teen pregnancies are very common in some parts of the world, and they are often associated with low income and cultural levels. The uneven legal rules for assisted fertilisation and the lack of systematic assessment of the kidney function point to the need for further research.

Despite elegant demonstrations for the role of sex hormones in vascular health and immunoregulation, the striking predominance in females of SLE, RA and SS remains unexplained relative to other systemic diseases, such as ANCA vasculitis and haemolytic-uraemic syndrome. Note that thrombotic thrombocytopenic purpura has a higher incidence in women, though this is likely due to the association with other conditions more common in women. The incidence of kidney involvement in SLE during pregnancy and similarities/differences in those with PE has not been well studied. The role of
different medications and responses to medications for autoimmune diseases relative to sex has also not been well studied.

More attention to similarities between conditions, the importance of sex hormones in inflammation, immune modulation and vascular health, may lead to important insights and clinical breakthroughs over time. If women are more likely to be living donors, at differential ages, does this impact both CVD risk, and risk for ESKD: have we studied this well enough, in the current era, with modern diagnostic criteria for CKD and sophisticated tools to understand renal reserve? Are the additional exposures that women have after living donation compounded by hormonal changes on vasculature as they age? And are the risks of CKD and PE increased in the younger female kidney living donor?

In the context of specific therapies for the treatment or delay of CKD progression, do we know if there are sex differences in therapeutic responses to ACEi/ARB? Should we look at dose finding/adjustments by sex? If vascular and immune biology is impacted by sex hormones as described earlier, do we know the impact of various therapies by level or ratio of sex hormones? In low-middle income countries how does changing economic and social cultures impact women’s health, and what is the nutritional impact on CKD of increasing predominance of obesity, diabetes and hypertension?

Summary

Women have unique risks for kidney diseases: kidney diseases, as well as issues related to access to care, have a profound impact on both the current and next generations. Advocating for improved access to care for women is critical to maintain the health of families, communities and populations.

Focused studies on the unique contribution of sex hormones, or the interaction of sex hormones and other physiology, are important to improve our understanding of the progression of kidney diseases. Immunological conditions, such as pregnancy (viewed as a state of tolerance to non-self) as well as SLE and other autoimmune and systemic conditions common in women, better studied may also lead to breakthroughs in understanding and care paradigms.

There is a clear need for higher awareness, timely diagnosis and proper follow-up of CKD in pregnancy. In turn, pregnancy may also be a valuable occasion for early diagnosis of CKD, allowing planning of therapeutic interventions.

On this occasion, World Kidney Day and the International Women’s Day 2018 are commemorated on the same day, offering us the opportunity to highlight the importance of women’s health and particularly their kidney health. On its 13th anniversary, World Kidney Day promotes affordable and equitable access to health education, healthcare and prevention for all women and girls in the world.

The coincidence of World Kidney Day and International Women’s Day offers an opportunity to develop and define best practices and future research agendas, and ultimately, to optimise the outcomes of all people living with or at risk for kidney disease.

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References


35 Low Birth Weight and Nephron Number Working Group. The impact of kidney development on the life


Supporting Information

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

Table S1. Adverse pregnancy outcomes in patients with chronic kidney disease (CKD) and in their offspring.
Recording patient bodyweight in hospitals: are we doing well enough?

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Key words
patient weight, hospital admission, medication prescribing.

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Abstract
Recording patient weight is a standard practice for all hospital admissions, with this measurement influencing other daily practices that rely on the delivery of safe and effective patient care. Patient weight is important in the areas of medication prescribing, fluid balance and assessment of nutrition. In particular, prescribing narrow therapeutic index medications may result in significant harm as a potential consequence of inaccurate dosing. Despite its importance, it is evident that bodyweight measurements are recorded in only 13.5–55% of hospital patients, in a variety of settings including the emergency department, intensive care unit, medical and surgical wards. Barriers to compliance of healthcare staff include additional workload, patient handling and availability of appropriate weighing equipment. Hospitals and patients would benefit from enhancing compliance with the systematic weighing of patients, staff training and removing barriers to performing this task.

Introduction
Recording accurate patient weight is a fundamental part of the initial patient assessment as it potentially influences a variety of clinical tasks during hospital admission (Table 1). This includes accurate prescribing, fluid assessment, nutritional and obesity screening and safe patient lifting practices. Most research regarding weighing of hospitalised patients is from the United States (US) and the United Kingdom (UK) with only limited data from Australia. Data reveal that in a variety of hospital settings, including the emergency department (ED), intensive care unit (ICU), medical and surgical wards, staff compliance with best practice of weighing patients ranges between 13.5 and 55%.

Prescribing medications
Errors in medication dose administration have the potential to lead to adverse outcomes. Doses are regularly calculated based on patient weight, particularly for medications with a narrow therapeutic index, in patients with renal dysfunction and in the paediatric population. There is a large discrepancy in the practice of weighing paediatric and adult patients, with the compliance of paediatric weight recording near 100%.

Despite the importance, recording of adult bodyweight is universally done poorly. A multi-centre study in the US revealed that only 65.7% of patients were weighed within the first 36 h of admission. Of those not weighed, 67% of patients were asked about their weight, and these estimations were more likely to vary from the actual weight by >5 lbs (2.27 kg). This inaccurate weight recording could potentially lead to adverse outcomes related to medication prescribing.

Narrow therapeutic index medications
Patient weight is often required to guide initial dosing of narrow therapeutic index medication such as thrombolytic agents, anticoagulants and antibiotics such as the aminoglycosides and vancomycin. A study across three hospitals in London tested the prevalence of weight recording in patients who were prescribed narrow therapeutic index antibiotics. Of the 8.8% of patients who were prescribed these medications, 34% did not have a recorded weight. In another UK study, only 64.5% of patients who had received gentamicin or low molecular weight heparin (LMWH) had their weight recorded. In an Australian setting, patients receiving heparin, enoxaparin or gentamicin were weighed approximately 25% of the
Increased risk of disease, medical complications and death.3 The recognition of obesity allows clinicians to discuss bodyweight with patients with a view to encouraging weight reduction, lifestyle changes and better health outcomes.

The intra-operative and post-operative complication risk in obese patients is higher than non-obese patients, suggesting that identification in the pre-operative setting may be a prognostic factor.19,20 Following moderate or major non-cardiac surgery, obese patients are at significantly higher risk of myocardial infarction (P = 0.001), wound infection (P = 0.001), nerve injury (P = 0.03) and urinary tract infection (P = 0.004).19 Weighing patients would provide an objective measurement to screen for these at-risk patients and allow for appropriate peri-operative preparation. Identification of obese patients is also important from a logistical perspective, because they may require specialised care in terms of technique, staffing and use of equipment such as bariatric beds and hoist transfers.

Nutritional assessment

Malnutrition is associated with multiple adverse patient outcomes including depression of the immune system, impaired wound healing, muscle wasting, extended hospital stay, higher treatment costs and increased mortality.21 Accordingly, malnutrition is an important risk factor to identify in patients admitted to hospital.

In the acute hospital setting, malnutrition is a highly prevalent condition, with Australian and international studies reporting rates of approximately 40% of admissions.21 There were similar findings in a study of residential aged care facilities in Australia, which found 43.1% of residents to be moderately malnourished and 6.4% severely malnourished.22 Patient weight has been validated as a part of many effective malnutrition screening tools.23 There is a correlation between more consistent weighing practices and a reduction in the prevalence of malnutrition in hospitalised patients.24

Volume status and fluid management

Fluid management is important in critically ill patients, with numerous studies showing an association between positive fluid balance and increased mortality.16,25,26 In specific medical conditions such as cardiac, liver and kidney failure, strict fluid balance during hospital admission aids in the prevention of clinical deterioration.16,25,26 The accurate and timely measurement of patient weights is essential in guiding fluid management in this select cohort where maintaining optimal volume status is critical.
Increasing weight in a haemodialysis patient can indicate fluid accumulation. A ‘dry weight’ reflects the lowest post-dialysis weight, and therefore the fluid balance each patient can tolerate without developing hypotension.27 Adhering to tight control of ‘dry weight’ over time in this cohort is thought to be associated with a significant reduction in the risk of cardiovascular mortality.28 Other studies have found an association between chronic fluid overload and increased mortality risk in haemodialysis patients.29,30

One method of fluid balance monitoring is through input/output balance charts, however these charts are time consuming and the accuracy of information is debatable with data often incomplete.31 Daily, and in some cases twice daily, measurement of patient weight is another marker of volume status, as most changes in weight over a short period of time are associated with change in body fluids.25 Use of daily weight measurements has been assessed in a variety of patient populations to aid clinical decision-making.32

Weight estimation in place of measurement

Several hospital-based studies across the UK and US have investigated the efficacy of weight estimation techniques compared with objectively measured weights and found that clinicians are generally poor at estimating weight.1,6,9–11

Hospital staff inaccurately estimate weight approximately 50% of the time, particularly in patients with low and high body mass index.3,6,9,10 Staff overestimate the weight of lighter patients and underestimate the weight of heavier patients, particularly among female patients.11 In contrast, patients more accurately estimate their own weight compared with hospital staff.4,6,11 In one US study, patients were nine times more likely than medical and nursing staff to estimate accurately their own weight.11 In another study in the UK, patients were 80% accurate at their own weight estimation compared to 39% of staff (P < 0.001).6 These data indicate that where possible a patient’s weight should be measured and not estimated.

Barriers to weighing patients in hospital

Additional workload

Of the barriers preventing staff from regularly recording patient weights during hospital admissions, the burden of additional workload, inadequate staffing and interruption to workflow are the most common reasons given (Table 2).2,12,14,35 A trial of different weight scales used in a Melbourne study drew complaints of extra workload to busy nursing staff, and concerns that the weight on the scales did not match personal visual estimates.14 The timing of patient weighing may also interfere with other nursing tasks, and is worth considering when implementing daily weighing into routine practice.35

Table 2 Barriers to weighing patients in hospital

<table>
<thead>
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<th>Barriers to weighing patients in hospital</th>
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<tr>
<td>• Burden of additional workload</td>
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<td>• Stress of manually handling patients</td>
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<tr>
<td>• Lack of effective weighing equipment</td>
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<tr>
<td>• Poor understanding of the importance of recording accurate weight</td>
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<tr>
<td>• Confusion due to multiple areas in the patient’s medical records to document weight</td>
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<tr>
<td>• Perceived patient distress</td>
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Difficulty handling patients

Nurses in an Australian study ranked lifting and weighing patients among their eight most stressful handling tasks, and that cognitively impaired and aggressive patients were the most difficult to weigh regularly.5 Other studies have found the burden of locating equipment too time consuming, and that asking the patient for their own weight estimate is more convenient.6,6 In other survey responses, staff have reported bed bound patients and very unwell patients as barriers to measuring weight.6

It is reasonable to acknowledge that not every patient can stand on scales and be easily weighed in every situation, such as patients in the intensive care unit (ICU), the elderly and those in post-operative care. The use of alternative weighing methods, such as bed scales and chair scales, may be used among patients who cannot independently stand or follow direction safely. In a Melbourne ICU study, the most efficient and economical method was using a bed weighing scale, where the patient does not need to move from the supine/semi-recumbent position. This could be an alternate method for hospitals with patients too unwell to move from bed.14

Variations in weighing equipment

Variation in the accuracy of weighing equipment may adversely confound clinical decision-making. A US study comparing 223 different scales for accuracy used across multiple healthcare centres found that scales calibrated within the previous year, scales used on carpeted floors and scales with less wear and tear were more precise.13 Other studies have found faulty equipment to be a common issue.2,4,5 A minimum standard for patient scale
accuracy in the UK has been implemented by the European Parliament. This legislation imposes a requirement in every hospital for a robust program of equipment testing and calibration, as well as basic staff training on how to weigh accurately and correctly different cohorts of patients.  

Inconsistent documentation

Recording of patient weights in multiple areas of documentation is commonplace in hospital admissions. Although perhaps not a direct barrier to the act of weighing patients, inconsistent documentation may create confusion among treating teams, leading to barriers in accurate weight recording and interpretation, and poor communication during patient admissions.  

If weight assessment and documentation are to be improved, hospital policies must be updated and streamlined with timely staff education to enable consistent and coherent weight documentation.

Opinion divergence: perceived lack of utility and patient distress

Some healthcare workers believe that weighing patients is either unnecessary or should be omitted depending on the state of the patient’s health. In an audit in 2009, nursing staff on a medical ward in the UK thought that weighing was unnecessarily invasive for the patient. Others have proposed that weighing patients may be distressing for the patient and would not change management. In a qualitative study in a UK hospice with terminally ill patients, staff did not want patients thinking about their weight during palliative care, with 55% declaring a desire not to weigh patients. This indicates that in areas of health such as end of life care, recording patient weight may be considered futile or unimportant. However, 98% of the patients in this study felt that getting weighed was not upsetting, 89% wanted to know if their weight was changing and 84% of patients wanted to be weighed at future hospital appointments. This may demonstrate a divergence between perceived inconvenience of weighing by staff and patients.

Limitations in existing data

Most of the available literature fails to identify direct correlation between actual adverse clinical outcomes as a result of failure to weigh patients as the sole causality factor. There are no blinded, randomised control studies in this area, and available studies suffer from biases that commonly occur in retrospective and non-blinded observational cohort studies. For example, patients may not have been weighed because they had more pre-existing co-morbidities confining them to bed, creating practical difficulties in facilitating the weighing process. Studies describing consequences of excess thrombolytic administration such as bleeding were underpowered and limited to single or few centres in one region, making it potentially difficult to generalise results to other populations.

Conclusion

While there is limited direct evidence of harm from failure to weigh patients, there is a greater overall benefit to patients if they are weighed when they access healthcare. These benefits are most pronounced in the areas of fluid balance, assessment of nutrition and medication prescribing. Excessive dosing of anticoagulation has been shown almost to double the risk of major bleeding and death. The choice of weighing equipment needs to be considered depending on patient case mix, as unique patient cohort characteristics likely require a modified approach equipment to selection. Availability of this equipment may help to remove the barriers to weighing patients in hospital. Institutions would benefit from staff training to improve compliance with weighing patients, and regular equipment calibration to maintain consistent and accurate measurements.

References

Flentje et al.


Climate change: allergens and allergic diseases
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Key words
pollen, spores, fungal, allergy, asthma, food hypersensitivity.

Abstract
Climate change has been described as the biggest global health threat of the 21st century. The atmospheric concentrations of greenhouse gases, such as carbon dioxide, methane and nitrous oxide, have increased significantly since the start of the Industrial Era around 1750, with much of this increase occurring over just the last 50 years or so. This is resulting in warming of the climate system as well as changes in precipitation and weather and climate extremes. These changes in climate are having wide-ranging impacts on the Earth’s physical, biological and human systems, including human health. It is these impacts of climate change on human health that are the focus of this paper, particularly the impacts on allergens and allergic diseases. Such impacts are particularly significant in many countries where the prevalence of such diseases is high and/or increasing. There is now compelling evidence that rising air temperatures and carbon dioxide concentrations are, in some plant species, resulting in increased pollen production and allergenicity and advancement and lengthening of the pollen season. Changes in extreme events, such as thunderstorms and tropical cyclones, will also have impacts on allergic diseases, with, for example, the flooding associated with tropical cyclones leading to proliferation of mould growth in damp homes. The article also considers a range of responses to these health threats, including greenhouse gas mitigation, and adaptation strategies, such as enhanced environmental monitoring and health surveillance and adequate planning for the future medical workforce.

Introduction
The Lancet recently stated that ‘Climate change is the biggest global health threat of the 21st century’,1 and with this in mind, it is particularly significant that 2016 was the warmest year on record – warmer than 2015, which was much warmer than 2014, which was warmer than all previous years in the modern global temperature record. The year 2016 was, of course, significant for many reasons, but is also of particular significance to this article; 21 and 22 November 2016 witnessed by far the most severe thunderstorm asthma event ever recorded, overwhelming emergency services and hospitals in Melbourne, Australia, with an estimated 3365 more public hospital emergency department respiratory-related presentations than expected and as many as nine deaths.3

This review explores the implications of climate change for human health, particularly for allergens and allergic diseases, and how this might be managed in clinical practice. We first outline the nature of climate change, particularly those aspects of it most relevant to allergens and allergic diseases. This is followed by a brief overview of the impacts of climate change on human health. We then describe the impacts of climate change on allergens and allergic diseases, focusing on allergic respiratory diseases and food allergy. We then outline several responses to these health threats.

What is climate change?
While climate change is perhaps most commonly considered to involve warming of the climate, and this is
Climate change involves a highly complex system consisting of the atmosphere, the hydrosphere (oceans, seas, rivers, fresh water lakes, underground water), the cryosphere (sea ice, snow cover, glaciers and ice sheets, frozen ground), the land surface and the biosphere (all living organisms). Human influence on the climate system is clear, and warming of the climate system is unequivocal.

The largest driver of climate change is the increase in the atmospheric carbon dioxide (CO$_2$) concentration since the start of the Industrial Era around 1750. The annual mean atmospheric CO$_2$ concentration in 2016 was 404.21 ppm, measured at the Mauna Loa Observatory in Hawaii. This is an increase of well over 100 ppm from the pre-industrial concentration of just 280 ppm. The increase in atmospheric CO$_2$ concentration from 1750 to the present has not been gradual, with two thirds of the increase occurring over just the last 50 years (since 1967). CO$_2$ is not the only greenhouse gas to have increased since 1750 due to human activity. The atmospheric concentrations of methane and nitrous oxide have also increased significantly, by about 150 and 20% respectively.

These increases in greenhouse gases have resulted in an uptake of energy by the climate system, which has led to warming. The average temperature of the Earth’s surface is about 14°C and has increased by almost 1°C over the past 100 years or so. Importantly, the extent of warming varies over the surface of the Earth, with some places warming less than this global average and others warming more. Projections of future climate change indicate that the global mean surface temperature will increase by a further 0.3–4.8°C by the end of this century relative to the period 1986–2005, depending on the greenhouse gas emissions scenario. Again, these future temperature increases will vary spatially, with mean warming over land being higher than over the ocean.

Many other aspects of climate have also changed and will continue to do so into the future. The changes in precipitation have been more complex than those in temperature, in that some regions have observed an increase in precipitation while some have observed a decrease in precipitation and yet others have experienced no change at all. Projections for the future indicate that the contrast in precipitation between wet and dry regions and between wet and dry seasons will increase.

Climate change also involves changes in extreme weather and climate events. Hot days and nights will be warmer and/or more frequent, and heat waves will be more frequent and/or longer lasting over most land areas. There will be increases in the frequency, intensity and/or amount of heavy precipitation in some regions. There is also evidence that thunderstorms and intense tropical cyclone activity may increase into the future.

The impacts of these many and varied changes in climate have been observed for some time now. Glaciers are shrinking, Arctic sea ice is thinning, the sea level is rising and oceans are becoming more acidic as they absorb some of the excess CO$_2$ from the atmosphere. Many plant and animal species have shifted their geographic ranges, seasonal activities, migration patterns, abundances and species interactions in response to climate change. Impacts are also occurring on what are referred to as human systems, of which human health is one. The following section outlines these impacts.

### Health impacts of climate change

The health impacts of global climate change will be widespread and will have variable effects depending on geographic region, socioeconomic status of a population and pre-existing population vulnerabilities. There are many consequences, mostly negative, for public health, and these have been summarised in global terms by the World Health Organisation (WHO) as threats to safe drinking water, adequate shelter, stable food source and clean air.

Threats to public health result from the major consequences of climate change:

- **a** increases in natural, weather-related disasters or major weather events that create havoc, with destruction of housing, dislocation of populations and threat of spreading disease;
- **b** changes in rainfall – in some areas excessive, leading to flooding, and in others a striking lack, resulting in prolonged drought and crop failure;
- **c** heat waves are associated with documented excess mortality. Increasing heat will also have important impacts on air quality and pollutant levels, and these are particularly threatening to children, the elderly and those with cardiovascular and respiratory disorders;
- **d** warmer temperatures and increased CO$_2$ have impacts on allergens and allergic diseases, such as asthma and allergic rhinosinusitis. These will be among the most important climate change influences on human health and are the focus of the remainder of this article.

### Aeroallergens and allergic diseases

A comprehensive review of the impacts of climate change on allergens and allergic diseases has been published recently. Through the effects of key climate change factors, we expect significant changes in exposure patterns to plants, pollen and fungi. In addition,
complex interactions between pollutants, dust storm material, thunderstorm events and allergens may be expected to impact respiratory health negatively as well. Respiratory allergic diseases, such as asthma and allergic rhinoconjunctivitis, have become very prevalent in many parts of the world over the last few decades. Therefore, there is a very large population at risk of significant allergic disease with any increase in pollen exposure and allergenicity. Furthermore, pollen allergy is also implicated in certain forms of food-allergic disorders, so changes in pollen distribution and allergenicity may be expected to impact these conditions as well.

Clinical evidence of the importance of pollen exposure in causation of allergic respiratory diseases comes from a variety of approaches, ranging from exploring the patterns of sensitisation to various pollen allergens to examining correlations between the pollen count and asthma exacerbations, usually measured by hospital attendances or admissions. Asthma exacerbations are an important parameter as they carry significant economic implications.

### Pollen production and allergenicity

There is now compelling evidence that rising temperatures and CO₂ levels impact plant and pollen production. For many plants, rising CO₂ levels represent an increase in a vital resource, and they respond accordingly with increased growth and reproduction and greater pollen yields. Singer et al., have shown that with increasing CO₂ levels, the major allergen from ragweed, Amb a 1, increases, although there is no change in total pollen protein level.

Ragweed, a native of North America, has been invading large areas of South America and Europe for the last few decades. It is a major cause of respiratory allergy. Hamaoui-Laguel et al., have used modelling frameworks that account for various factors under high-end and moderate climate and land-use change scenarios to predict airborne ragweed pollen concentrations in Europe in the future. Their modelling shows that, by 2050, airborne ragweed pollen concentrations will be about four times higher than they are now, almost certainly increasing the incidence and prevalence of ragweed allergy. Indeed, in subsequent work, it has been found that sensitisation to ragweed will more than double in Europe, from 33 to 77 million people, by 2041–2060; that the greatest proportional increases will occur where sensitisation is uncommon (e.g. Germany, Poland, France) and that higher pollen concentrations and a longer pollen season may also increase the severity of symptoms. While ragweed is not an important allergen in Australia at present, it has been introduced and is likely to spread and become a problem if effective eradication measures are not in place.

### Pollen seasons

Phenology is the study of the influence of climate on periodic plant and animal life-cycle events. There are some long-term phenological records in many European countries, and these demonstrate measurable changes occurring in recent decades. Flowering is particularly sensitive to temperature over the preceding month. Fitter and Fitter have demonstrated an average 4.5-day advancement in the first flowering date for nearly 400 British plant species over the 1990s compared with the previous four decades. Menzel has examined data from a Europe-wide network, the International Phenological Gardens, and reports that the average annual growing season has lengthened by approximately 11 days since the 1960s.

In countries where there are long-term aerobiological survey data, it is possible to examine trends in airborne pollen and fungal spore counts. The trends are by no means uniform but vary with geographical location and plant type. Analysis of these data makes it possible not only to track changes in the pollen season but also to examine changes in flowering patterns in flowering phenology, one of the most valuable indicators of climate change impact.

Ariano et al., had a unique opportunity to study variations in pollen levels and allergic sensitisation in Western Liguria, Italy, because of the existence of almost three decades of pollen monitoring and meteorological variable data and skin test and clinical data from residents in the region. They describe a progressive increase in the duration of the pollen season for *Parietaria* (+85 days), olive (+18 days) and cypress (+18 days). All pollen monitored, except for grasses, showed an increase in total counts. They report an increase in the percentages of patients sensitised to pollen over these years, whereas sensitisation rates to the house dust mite remained stable.

Consistent with the findings of Ariano et al., a 30-year (1982–2011) olive pollen record from Spain has shown a trend towards increasing pollen production, most likely caused by longer flowering periods as a result of higher temperatures.

### Fungal exposure and allergy

Fungi are a large and diverse group of eukaryotic organisms that have complex metabolisms, secreting numerous enzymes into their surroundings. Many of these are well-described allergens. Other chemicals include...
ergosterol, which can be used as a measure of fungal biomass; constituents of cell walls, such as β-glucans that have been shown to cause respiratory symptoms, itching and fatigue in a dose-dependent manner and mycotoxins, which are low molecular weight organic compounds important in agriculture (e.g. aflatoxin). The role of the latter in producing human disease in domestic environments is far more contentious. Volatile fungal metabolites are responsible for the musty smell associated with fungal growth.22

Adverse health effects from fungal exposure can occur by a variety of mechanisms, including infection, allergy, irritation and toxicity, depending on the nature and dose of the exposure. Infection may be seen in normal and immune-compromised patients. Fungal components, such as β-glucan, may produce effects through activation of the innate immune system or through T cell and other mechanisms. Allergic sensitisation to fungi is an important risk factor for allergic asthma, and fungal exposure has been linked to asthma exacerbations and hospital presentations23 as well as a described association with asthma mortality.24 In addition to allergic rhinitis and asthma, fungal exposure has been linked to conditions like allergic broncho-pulmonary aspergillosis, hypersensitivity pneumonitis, allergic fungal sinusitis and atopic dermatitis.

Increased flooding in many areas of the world is seen as a consequence of climate change. Flooding leading to long-term dampness in residential dwellings promotes fungal growth. In the aftermath of Hurricane Katrina in New Orleans, USA, high indoor and outdoor fungal counts were noted.25 Increased moisture along with higher temperatures and CO₂ levels encourage fungal growth.

Food allergy

Food allergy has become a very significant public health concern as 4–8% of children and 3–4% of adults in Westernised countries have a food allergy.26–27 Aeroallergens, and sensitisation to them, are important in some expressions of food allergy.

IgE-mediated food allergy to common foods, such as cow’s milk, egg, soy, nuts, wheat and seafood (known as Class I food allergens), may result from sensitisation through the gastrointestinal tract. A less well-recognised form of food allergy may occur as a result of primary sensitisation to homologous pollen allergens through the respiratory tract, causing reactivity to cross-reactive food allergens (Class II allergens).18 Global differences in food sensitisation patterns have been particularly observed for these plant food allergens, whereby differences in allergenic plant distribution, agriculture and dietary patterns determine the predominant pattern of pollen and food allergy.18 For instance, in Europe, prevalence of plant food allergy is significantly influenced by sensitisation to particular proteins in birch pollen, such as Bet v 1 and Bet v 2, while in the Mediterranean region, there is a higher sensitisation rate to prolins and non-specific lipid transfer proteins.28 A recent study has shown differences in the pattern of allergen reactivity causing peanut sensitisation across different geographic regions, and these differences are largely determined by aeroallergen exposure.29 Thus, it is likely that changes in climate that result in altered distribution of various allergic plants may, in time, bring about a change in the pattern of food allergy, especially that caused by plant food allergens.18 Furthermore, there is now limited experimental evidence that increasing CO₂ concentrations may directly alter the allergenicity of some plant-derived foods, with a recent study showing increased allergen concentration in peanut when grown under such conditions.30

Eosinophilic oesophagitis has become a commonly recognised condition in children with dysphagia, with antigen exposure being the driving force for the eosinophilic inflammation seen in this condition.31 While food allergens are the obvious major allergens involved in this process, there are data to suggest that aeroallergen exposure is capable of triggering eosinophilic inflammation either because of the swallowed fraction or because of ingestion of foods cross-reacting with pollen allergens. The potential role of aeroallergens in provoking paediatric eosinophilic oesophagitis has recently been studied by Fahey et al.12

Response to climate change health threats

For years, a reduction in greenhouse gases has been central to our approach to managing the effects of climate change, and for the sake of planet and human health, these efforts must continue and grow much stronger. Immediate and sustained reduction of all pollutants, coal-burning technologies and transport-related pollution must be enabled. However, there are many indicators that the rising greenhouse gases have already brought about significant changes that must be addressed and managed. This realisation has shifted the focus from purely attempting to reduce greenhouse gases to one of managing the many aspects of health impacts caused by the changing climate. The WHO has made adaptation a critical component of the United Nations Framework Convention on Climate Change (UNFCCC), with particular emphasis on planning strategies for the developing world where the impact on population health will be the greatest.13
Central to endeavours for managing climate change and associated health impacts is the establishment of precise, ongoing measurements of all those parameters demonstrated to be important for their impacts on human health. For instance, in the case of aeroallergen impact on respiratory health, the studies on influences of climate change on plant growth and distribution, and pollen production, have come predominantly from the Northern Hemisphere. In Australia, until recently, there has been no systematic aerobiological monitoring. This is beginning to be addressed, with the establishment of a national pollen monitoring service within a partnership known as the AusPollen project. Long-term, longitudinal studies to map allergenic pollen and fungi distribution are necessary to help understand the patterns of respiratory allergy and to plan for times of peak exposures and likely hospital presentations. The significance and importance of this have been noted very recently in the context of the November 2016 Melbourne thunderstorm asthma event.

This paper has highlighted the important role of aeroallergens in driving inflammation in many allergic conditions, so the management of aeroallergen sensitisation and allergy will be an important aspect of planning specific mitigation strategies given the exposure increases we can expect with climate change. Although allergic conditions are some of the most common afflictions in medical practice, highly trained specialists in this field are few in number. Endeavours to upskill the general medical workforce in the recognition and management of allergic disorders will be an important component in any mitigation strategy. Immunotherapy, as a treatment strategy for those expressing the clinical consequences of inhalant allergy, has been in use for a century. Improvements in allergen characterisation, methods of delivery and length of treatment programmes will enhance its utility in addressing some of the morbidity produced by aeroallergen exposure.

Conclusion

The medical community has engaged in understanding and managing risks within the health arena for many decades. As such, all members of the medical community have roles to play in managing responses to climate change, from data collection and mitigation to adaptation. We need to be advocates for rapid and sustained reductions in greenhouse gas emissions, leading by example in institutions like hospitals. Alongside these efforts must be planning and adoption of strategies for adaptation to the inevitable climate change factors that so powerfully impact many facets of health.

Adaptation strategy must incorporate improved and effective monitoring of the many variables and consequences associated with climate change factors. This includes accurate measures of particulates and pollutants; precise records of infection transmission and vector populations and accurate, long-term aerobiological monitoring to map changing patterns of pollen and mould spore distribution.

Another vital aspect is appropriate forward planning for workforce diversity that will be required to manage specific challenges, some of which have been outlined in this paper. Finally, it is imperative that the more affluent communities assist those in developing countries to achieve these same goals as they are likely to bear the consequences of climate change to an even greater extent than those in affluent communities.

References


8 Beggs PJ, ed. Impacts of Climate Change on Allergens and Allergic Diseases.
Katelaris & Beggs


12 Ziska LH, Bunce JA. Predicting the impact of changing CO₂ on crop yields: some thoughts on food. New Phytool 2007; 176: 607–18.


EVOLVE: The Australian Rheumatology Association’s ‘top five’ list of investigations and interventions doctors and patients should question

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Key words
EVOLVE, evidence-based practice, implementation, low-value care, rheumatology.

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Abstract

Background: The EVOLVE (evaluating evidence, enhancing efficiencies) initiative aims to drive safer, higher-quality patient care through identifying and reducing low-value practices.

Aims: To determine the Australian Rheumatology Association’s (ARA) ‘top five’ list of low-value practices.

Methods: A working group comprising 19 rheumatologists and three trainees compiled a preliminary list. Items were retained if there was strong evidence of low value and there was high or increasing clinical use and/or increasing cost. All ARA members (356 rheumatologists and 72 trainees) were invited to indicate their ‘top five’ list from a list of 12-items through SurveyMonkey in December 2015 (reminder February 2016).

Results: A total of 179 rheumatologists (50.3%) and 19 trainees (26.4%) responded. The top five list (percentage of rheumatologists, including item in their top five list) was: Do not perform arthroscopy with lavage and/or debridement for symptomatic osteoarthritis of the knee nor partial meniscectomy for a degenerate meniscal tear (73.2%); Do not order anti-nuclear antibody (ANA) testing without symptoms and/or signs suggestive of a systemic rheumatic disease (56.4%); Do not undertake imaging for low back pain for patients without indications of an underlying serious condition (50.8%); Do not use ultrasound guidance to perform injections into the subacromial space as it provides no additional benefit in comparison to landmark-guided injection (50.3%) and Do not order anti-double-stranded DNA antibodies in ANA negative patients unless the clinical suspicion of systemic lupus erythematosus remains high (45.3%).

Conclusions: This list is intended to increase awareness among rheumatologists, other clinicians and patients about commonly used low-value practices that should be questioned.

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Conflict of interest: None.
Introduction

The cost of healthcare in Australia is growing faster than population growth. For example, there was a near doubling of health expenditure over the decade 2001–2002 to 2011–2012. This has placed an increased focus on healthcare quality, affordability and value. The Royal Australasian College of Physicians’ (RACP) EVOLVE (evaluating evidence, enhancing efficiencies) initiative is a clinician-led partnership between the College and its specialty societies. It aims to drive safer, higher-quality patient care through identifying and reducing low-value medical care, defined as tests, treatments or procedures that are overused, inappropriate or of limited effectiveness and/or potentially harmful.

Modelled on Choosing Wisely initiatives in the United States and other countries,3 and working in conjunction with Choosing Wisely Australia,4 specialist physicians from over 20 medical specialties have completed or are developing their EVOLVE ‘top five’ lists of low-value clinical practices. The guiding principles of EVOLVE are that the ‘top five’ list should be within or significantly impact the specialists’ domain of practice with the potential to make a real impact in reducing low-value care; the practices should be either growing in use or currently commonly used and use of the Delphi consensus method,5 as the overarching methodology for identifying a ‘top-five’ list.

In this article, we present the Australian Rheumatology Association’s (ARA) ‘top five’ list of low-value practices.

Methods

The EVOLVE ARA working group comprised 19 rheumatologists and 3 advanced rheumatology trainees formed after a call for interested ARA members. At a face-to-face meeting in 2015, the guiding EVOLVE principles were discussed and it was agreed that items should be included if they were either primarily a rheumatologist issue or an issue that rheumatologists should advocate for on behalf of their patients.

A preliminary list of low-value clinical practices was created based upon the working group’s clinical experiences, as well as consideration of potentially relevant items identified from lists generated by others.6–10 The working group reduced the initial list to 12 items, noting that some items included multiple components. Two items were excluded (Do not prescribe bisphosphonates for patients at low risk of fracture and Do not perform whole body bone scans for diagnostic screening for peripheral and axial arthritis in the adults), as these were not considered relevant to the Australian context.

Small teams for each topic were formed to review the evidence and determine if the preliminary list of low-value practices met all of the following criteria:

1 Strong evidence of low-value clinical practice from a literature review and
2 Evidence of high or increasing clinical use and significant and/or increasing cost to the Australian community based upon publicly available Medicare Benefits Schedule (MBS) item usage and cost data relating to each statement from 2004 to 2015.11

Medicare Statistics provides data for MBS item numbers divided by the number of Medicare participants enrolled at the end of each month. For this project, usage data are expressed as number of services per financial year and costs are expressed as total benefits paid out for these services by financial year. The number of services and costs included in the Medicare Statistics data only relate to services that are performed by a registered provider, qualify for the Medicare benefit and for which a claim has been processed by Medicare Australia. They do not include services provided by hospital doctors to public patients in public hospitals or services that qualify for a benefit under the Department of Veterans’ Affairs National Treatment Account. Another important caveat of MBS data is that some single items can be used for multiple indications and the specific indication for which that item is used is not collected. For example, while there are MBS item numbers for ultrasound-guided injections, these do not differentiate between ultrasound-guided injections for different body parts. In most, but not all instances we excluded item numbers for diagnostic imaging if the site being imaged was not specified.

One item, ‘Do not order an HLA-B27 unless spondyloarthritis is suspected based on specific signs or symptoms’, was removed from the list after the review revealed it did not fulfill the criteria of high or increasing usage or high cost in Australia. Following review of the evidence, a new item was included: ‘Do not order anti-neutrophil cytoplasmic antibodies (ANCA) testing for diagnosis of vasculitis unless one of the consensus guideline indications is present’. We retained two items, ‘Do not use ultrasound guidance to perform injections in the subacromial space (or trochanteric bursa), as it provides no additional benefit in comparison to landmark-guided injection’, because even though it was not possible to extract the exact number and cost of these subsidised ultrasound-guided injections, consensus among the working group was that a large and increasing number of ultrasound-guided injections is being performed (inappropriately) into these sites.
The working group refined the ‘do-not-do’ statements and wrote brief summaries of the evidence in support of it being a low-value clinical practice using the National Health and Medical Research Council (NHMRC) recommendations for summarising the level of evidence, strength of recommendation and quality. An anonymous survey was created in SurveyMonkey. All ordinary (356 rheumatologists) and associate (72 rheumatology trainees) ARA members were invited to participate through email on 10 December 2015 with a reminder sent 17 February 2016. The ARA Board approved the survey and ethical approval was not sought.

Respondents were provided with the survey purpose and background information about EVOLVE, presented with the 12 proposed recommendations for not undertaking a particular test, treatment or procedure and a summary of the evidence for each recommendation. They were asked to select the five recommendations for which they considered the evidence to be the strongest. They could also provide comments for any of the statements in free text. Finally, they were asked to provide some demographic and clinical practice details: gender, setting in which the majority of hours are worked (public, private, academic, retired and other), fellowship status (fellow for <10, 10–20, 21–30 or >30 years) and practice location (urban/metropolitan, large rural centre, small rural centre, remote). For the purposes of our ‘top five’ list we excluded trainee responses.

Table 1 presents the proportion of rheumatologists who put each of the 12 statements into their ‘top five’ list in order of ranking. Endorsement of individual statements ranged from 20.7 to 73.2% of respondents. The highest endorsement was for not performing arthroscopic treatments for knee osteoarthritis and/or degenerative meniscal tears (73.2%), while over half endorsed not performing anti-nuclear antibody (ANA) testing for patients without rheumatic symptoms (56.4%), imaging for low back pain in those without specific indications (50.8%) and ultrasound guidance for shoulder injections (50.3%).

Nearly all of the comments indicated that respondents would have liked to endorse more than five statements. Trainee responses were similar with four of the same recommendations chosen in the top five although there was even stronger endorsement for not performing arthroscopic treatments for knee osteoarthritis and/or degenerative meniscal tears (84.2%) and not performing ANA testing for patients without rheumatic symptoms (73.7%).

Results

Respondents included 179 rheumatologists (50.3% response rate) and 19 trainees (26.4% response rate). The majority of rheumatologists were male (n = 115, 64.3%, 4 missing responses) and just over half worked primarily in private practice (n = 95, 53.1%, 5 missing responses).

Table 1 presents the proportion of rheumatologists who put each of the 12 statements into their ‘top five’ list in order of ranking. Endorsement of individual statements ranged from 20.7 to 73.2% of respondents. The highest endorsement was for not performing arthroscopic treatments for knee osteoarthritis and/or degenerative meniscal tears (73.2%), while over half endorsed not performing anti-nuclear antibody (ANA) testing for patients without rheumatic symptoms (56.4%), imaging for low back pain in those without specific indications (50.8%) and ultrasound guidance for shoulder injections (50.3%).

Nearly all of the comments indicated that respondents would have liked to endorse more than five statements. Trainee responses were similar with four of the same recommendations chosen in the top five although there was even stronger endorsement for not performing arthroscopic treatments for knee osteoarthritis and/or degenerative meniscal tears (84.2%) and not performing ANA testing for patients without rheumatic symptoms (73.7%).
The top five recommendations together with a summary of the evidence that they are a low-value test or treatment and their current use/cost is summarised below. The remaining seven recommendations are described in Appendix I (Supporting information).

**Recommendation 1: Do not perform arthroscopy with lavage and/or debridement or partial meniscectomy for patients with symptomatic osteoarthritis of the knee and/or degenerate meniscal tear**

Strength of recommendation: A
NHMRC level of evidence: I
Category of evidence: Ia

There is consistent evidence to indicate that arthroscopic lavage and/or debridement to treat people for symptomatic knee osteoarthritis and/or partial meniscectomy for patients with a degenerate meniscal tear (with or without underlying osteoarthritis), is no more effective than placebo surgery or non-operative alternatives.\(^{14-19}\) There appears to be a high rate of conversion from knee arthroscopy to total knee arthroplasty, which rises with increased age, further suggesting arthroscopic surgery should be avoided in people over the age of 50 years.\(^{20-22}\) Additionally, arthroscopy is associated with peri- and post-operative risks and considerable cost.\(^{18,23}\)

To determine the trend in performance of knee arthroscopic treatment for knee osteoarthritis over time we considered five of nine MBS codes for knee arthroscopic washout, debridement and/or partial meniscectomy (Fig. 1). In total these item numbers, in people with private health insurance, increased in usage from 2004 to 2012 financial years, then appeared to plateau, and reduced by 5.9% between 2012 and 2015. Over the entire period there was an almost 2% p.a. increase. The total benefit paid out for these services was $17.3 million in 2004 and almost $27.1 million in 2015, corresponding to an annual growth rate of 4.15%.

**Recommendation 2: Do not order ANA testing in patients without symptoms and/or signs suggestive of a systemic rheumatic disease**

Strength of recommendation: B
Category of evidence: III-2

ANAs are present in healthy individuals and ANA testing is only useful in patients with symptoms and/or signs of a rheumatic disease where it can aid in the confirmation or exclusion of systemic connective tissue diseases. ANA testing has a very high negative predictive value for excluding connective tissue diseases. However a positive ANA does not have a high positive predictive value for diagnosing these conditions in isolation and further sub-serology testing is needed to diagnose accurately and classify these conditions.\(^{24,25}\)

Despite guidelines and recommendations not to perform an ANA test in patients without symptoms and/or signs suggestive of a connective tissue disease,\(^{26-30}\) there has been a steady increase over the last decade in the number of MBS-funded ANA tests ordered (Fig. 2). The total benefits paid out for these services has increased from $7.76 million in the 2004 financial year to $10.96...
million in the 2015 financial year, corresponding to an annual growth rate of 3.2%.

**Recommendation 3: Do not undertake imaging for low back pain in patients without indications of a serious underlying condition**

Strength of recommendation: A  
NHMRC level of evidence: I  
Category of evidence: Ia

Most episodes of low back pain (~90%) do not require imaging. Imaging may identify irrelevant incidental findings and increase the risk of exposure to unnecessary and sometimes invasive treatment, in addition to increasing costs.31–33 For patients with low back pain and no suggestion of serious underlying conditions there are no significant differences in pain or disability outcomes between immediate imaging as compared with usual care without imaging.34,35

MBS-funded imaging for low back pain has been increasing consistently since 2004 primarily due to increased numbers of computed tomography (CT) and magnetic resonance imaging (MRI) scans (Fig. 3). The total MBS benefit paid out for MRI imaging has grown from $14.76 million in 2004 to almost $27.96 million in 2015, an annual growth rate of almost 6%. The total benefit paid out for the other imaging modalities of CT imaging and radiography has also grown from $58.4 million in 2004 to $99.08 million in 2015, an annual growth rate of 4.9%.

**Recommendation 4: Do not use ultrasound guidance to perform injections into the subacromial space, as it provides no additional benefit in comparison to landmark-guided injection**

Strength of recommendation: A  
NHMRC level of evidence: I  
Category of evidence: Ia

Currently there is no high quality evidence to support the superiority of ultrasound-guided subacromial injections compared with injections guided by landmarks alone. Based upon moderate evidence from five trials, a Cochrane review was unable to find any advantage of ultrasound-guided injection over either landmark-guided or intramuscular injection.36 These results are consistent with a more recent trial.37 In view of the currently available data and the significant added cost, there is little clinical justification in using ultrasound to guide injections for shoulder pain.
The exact number and costs of subsidised ultrasound-guided injections into the subacromial space are unknown as there are two MBS item numbers that include an ultrasound-guided intervention and neither specify a body site. We consider that a substantial number of these procedures are likely to have been performed for shoulder pain. There has been an annual increase of 26.8% in the number of ultrasound-guided injections for the period 2004–2015 (Fig. 4). In the 2014/2015 financial year the total benefits paid through the MBS for ultrasound-guided injection was almost $27.5 million.

As a comparison the total benefits paid through the MBS for landmark-guided joint injections (MBS items 50124 and 50125) in the 2008/2009 financial year was $12.8 million. These were removed from the MBS on 1 November 2009 due to a Budget decision by the government that these services are minor and routine in nature and can be delivered as part of a standard consultation. While removal of this MBS item may have resulted in a reduction in landmark-guided injection in primary and secondary care, it may have also contributed to the observed increase in more expensive image-guided injections. Several respondents made comments about the lack of reimbursement for landmark-guided injection, subsequent deskilling of GPs, long wait times for public rheumatology clinics, and radiologist-driven self-referrals as possible reasons for the increase in image-guided injection.

**Figure 4** Medicare Benefits Schedule (MBS)-funded ultrasound-guided injections for all musculoskeletal indications in Australia from 2004 to 2015. (MBS item numbers included in this figure. 55850 and 55851: Musculoskeletal cross-sectional echography, in conjunction with a surgical procedure using interventional techniques, inclusive of a diagnostic musculoskeletal ultrasound service, where the referring practitioner has indicated on a referral for a musculoskeletal ultrasound that a ultrasound guided intervention be performed if clinically indicated.) (——), 55850 and 55851.

**Figure 5** Medicare Benefits Schedule (MBS)-funded dsDNA testing in Australia from 2004 to 2015. (MBS item numbers included in this figure. 71099: Double-stranded DNA antibodies – quantitation by one or more methods other than the Crithidia method.) (——), 71099.

**Recommendation 5: Do not order anti-double-stranded (ds) DNA antibodies in ANA negative patients unless clinical suspicion of systemic lupus erythematosus (SLE) remains high**

Strength of recommendation: B

Category of evidence: III-2

International recommendations advise testing for anti-dsDNA antibodies only after detecting a positive ANA in patients with symptoms consistent with SLE. In patients who are ANA negative, anti-dsDNA should only be ordered in clinical situations where the pre-test probability of SLE is very high. Where positive, repeating anti-dsDNA antibodies titres is a useful test for monitoring disease activity, especially in lupus nephritis.

The number of MBS funded anti-dsDNA tests performed over 2004–2015 has steadily increased (Fig. 5) and the total benefits paid out for these tests more than doubled in the last decade from $2.1 million dollars in 2004 to $4.4 million dollars in 2015. This amounts to an average per annum growth of almost 7%. There are no epidemiological data suggesting that the incidence of SLE is rising. For example over roughly the same time period for which hospital separations data are available (2004–2014), the number of hospital separations with a principal diagnosis of SLE increased by less than 2.8% p.a.

**Discussion**

In this paper, we report the top five evidence- and consensus-based recommendations for tests and
procedures that Australian rheumatologists consider to be low-value care. An additional eight recommendations, while not included in the top five, were also endorsed by a significant number of rheumatologists. The most endorsed recommendation regarding arthroscopy osteoarthritis of the knee and/or degenerate meniscal tear is consistent with the recently launched Australian Clinical Care Standards for Osteoarthritis of the Knee, as well as a new clinical practice guideline published in the BMJ.

While we also include similar recommendations regarding ANA, ENA, dsDNA testing and frequency of BMD monitoring to some other countries, other recommendations were not transferrable to the Australian context. For example items, such as testing for Lyme disease and prescribing biologic agents prior to methotrexate were not deemed applicable to Australia due to differences in disease prevalence and mandated Medicare restrictions. This highlights the importance of creating recommendations based on local clinical practices.

Conclusion

In order for our ‘top five’ recommendations to be implemented into daily practice, consideration of enablers and barriers will be required. As a first step we intend to disseminate our recommendations widely to clinicians through peer-review publication, news sites, conferences and presentations; and to consumers through the use of social media, such as twitter. Additionally, some of our recommendations may be supported by other initiatives that are already taking place, such as the MBS review, and new models of care for back pain.

References


3 Choosing Wisely Canada. Toronto: University of Toronto, Canadian Medical Association, St Michael’s, 2015 [cited 2017 Sep 18]. Available from URL: http://choosingwiselycanada.org


13 SurveyMonkey Inc. PA, California, 2017 [cited 2017 Sep 18]. Available at URL: http://www.surveymonkey.com


21 Wai EK, Kredier JJ, Williams JI. Arthroscopic debridement of the knee for osteoarthritis in patients fifty years of age or older: utilization and


Supporting Information

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

Appendix S1. Recommendations included in the survey considered to be low-value care, but did not make the ‘top five’ recommendations.
Underappreciation of non-alcoholic fatty liver disease by primary care clinicians: limited awareness of surrogate markers of fibrosis

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Key words
non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, general practice, transient elastography, Enhanced Liver Fibrosis test.

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is a common cause of incidental liver test abnormalities. General practitioners (GP) have a key role in identifying people with NAFLD at risk of significant liver disease. Recent specialist guidelines emphasise the use of fibrosis algorithms or serum biomarkers rather than routine liver tests, to assess advanced fibrosis.

Aim: To evaluate primary care clinicians’ current approach to diagnosis, management and referral of NAFLD.

Methods: A cross-sectional survey of primary care clinicians was undertaken through a structured questionnaire about NAFLD. A convenience sample of general practice clinics and general practice conferences in Metropolitan Brisbane and regional south east Queensland was selected.

Results: A total of 108 primary care clinicians completed the survey (participation rate 100%). Fifty-one percent of respondents considered the prevalence of NAFLD in the general population to be ≤10%. Twenty-four percent of respondents felt that liver enzymes were sufficiently sensitive to detect underlying NAFLD. Most respondents were unsure whether the Fibrosis 4 score (62.7% unsure) or Enhanced Liver Fibrosis score (63.7% unsure) could help to identify advanced fibrosis or cirrhosis. Although 47% of respondents said they would refer a patient to a Gastroenterologist/Hepatologist if they suspect the patient has NAFLD, 44.1% do not make any referrals. Of concern, 70.6% of clinicians said they were unlikely to refer a patient to Hepatology unless liver function tests are abnormal.

Conclusion: Our findings demonstrate that many primary care clinicians underestimate the prevalence of NAFLD and under-recognise the clinical spectrum of NAFLD and how this is assessed.

Introduction

Non-alcoholic fatty liver disease (NAFLD), encompassing both simple steatosis and non-alcoholic steatohepatitis (NASH), is a condition characterised by excessive fat accumulation in the liver in the presence of metabolic risk factors and the absence of significant alcohol intake, or other causes of hepatic steatosis. The diagnosis of NASH relies upon a liver biopsy to demonstrate liver cell injury and inflammation. The prevalence of NAFLD is increasing in association with the widespread presence of obesity and type 2 diabetes1,2 and is now the most common cause of incidental liver test abnormalities in primary care.3

A study of over 1000 adult patients from eight primary care practices in the UK reported that abnormal liver function tests were commonly found incidentally during routine review of other chronic diseases, such as diabetes, cardiovascular disease and hypertension, and that
NAFLD accounted for over 25% of cases. Of concern, a study from a single Veterans Administration primary care centre showed that most patients at high risk of NAFLD were not being acknowledged or evaluated for this condition. Among 251 patients with NAFLD identified by the study investigators, only 21.5% had a diagnosis of NAFLD in primary care, 14.7% were counselled about diet and exercise and 10.4% were referred to a specialist. The study found that the only factors associated with receiving NAFLD-related care were the magnitude (with at least one alanine aminotransferase (ALT) value >80 IU/mL) and proportion (where ≥50% of a patient’s ALT values were >40 IU/mL) of ALT elevation.

Among people with NAFLD, recognition of advanced liver fibrosis is important because these patients may require specialist care and surveillance for liver cancer and liver decompensation. Most people with NAFLD have traditional normal-range liver blood tests and liver enzyme levels do not reflect the presence or severity of necroinflammation or fibrosis. The recently released UK National Institute of Clinical Excellence guidelines (NAFLD: assessment and management) advocate that routine liver blood tests alone should not be used to rule out NAFLD nor identify advanced fibrosis in people with NAFLD. Clinical practice guidelines for the diagnosis and management of NAFLD produced by international subspecialist committees recommend that ‘... Surrogate markers of fibrosis (NAFLD fibrosis score (NFS), Fibrosis 4 test (FIB-4), Enhanced Liver Fibrosis (ELF) test or FibroTest) should be calculated for every NAFLD patient, in order to rule out significant fibrosis (≥F2). If significant fibrosis cannot be ruled out, patients should be referred to a Liver Clinic for transient elastography ...’. Both the NFS and FIB-4 have a high negative predictive value, and low to no cost as they are calculated from routine blood tests (platelets, albumin, ALT and aspartate aminotransferase (AST)), age and body mass index (BMI) and can be run repeatedly without additional costs. The commercially available ELF test is calculated from combining three measured direct markers of liver matrix metabolism in serum. The ELF panel has good diagnostic accuracy for advanced fibrosis and has been shown to predict disease progression and the development of liver-related clinical events in patients with chronic liver disease. In Australia, the FibroTest is currently only available in a research capacity. Transient elastography (TE) provides a non-invasive assessment of liver fibrosis; however, this technology is not ideal for stratifying liver disease severity in the community, as it requires specialist expertise to obtain and interpret data.

Primary care clinicians have a key role in identifying patients with NAFLD who are at risk of significant liver disease and who may require specialist referral for further evaluation, or closer management of metabolic comorbidities and lifestyle interventions. However, it is currently unclear whether GP are aware of the recommendations regarding NAFLD risk stratification and management. We have previously shown that fatty liver and abnormal liver tests accounted for around 10% of referrals for hepatology outpatient consultation at a major tertiary referral hospital. Clinical information provided by referring clinicians was often incomplete and only a minority of referrals provided information about BMI or alcohol intake. There are no current Australian guidelines for NAFLD management in primary care, although the RACGP website (http://www.racgp.org.au/afp/2013/july/fatty-liver-disease/) contains a practical guide and algorithm for management of suspected NAFLD.

The purpose of this study was to assess primary care clinicians’ current understanding of NAFLD, along with their approach to diagnosis, management and criteria for referral. In order to address this, a cross-sectional survey of primary care clinicians from the greater Brisbane area was undertaken through a structured questionnaire about NAFLD.

### Methods

A cross-sectional study was conducted in south-east Queensland between August 2016 and March 2017. A convenience sample of general practice clinics and general practice conferences in metropolitan Brisbane and regional south east Queensland were selected. All primary care clinicians who attended general practice unit meetings or the conferences were invited to participate in the study.

The self-administered structured survey (available on request) developed by a research group (comprised of a hepatologist, epidemiologist and GP) for this study consisted of a series of closed-ended questions and one open-ended question. The survey was divided into four parts: (i) a brief introductory paragraph defining NAFLD and the spectrum of disease, including simple steatosis and NASH; (ii) a short demographic section comprising variables, such as Practice postcode, level of appointment, an estimate of the number of different patients seen per week, and an estimate of the proportion of subjects with NAFLD within their patient population; (iii) questions assessing the respondents’ knowledge about the prevalence of NAFLD, risk factors and perceptions about morbidity, diagnosis, risk stratification and treatment and (iv) respondents were asked about the referrals they made to hepatology services for investigation or management of NAFLD/NASH.
Face and content validity of the survey was assessed by delivering the questionnaire to three GP to determine whether they understood the questions and thought that the content of questions was relevant. Retest reliability was not assessed as it was not feasible to deliver the questionnaire to the same primary care clinicians twice due to their busy schedules.

This study was approved by the Princess Alexandra Hospital and The University of Queensland Human Research Ethics Committees (HREC/15/QPAH/301; UQ:2015001047).

Statistical methods
Basic descriptive details (total numbers and percentages) are presented. Continuous variables were summarised as mean (standard error of the mean) and median (range). The Chi-squared test was used to compare categorical variables and Student’s t-test to compare continuous variables. spss version 24.0 (spss, Chicago, IL, USA) was used for all analyses and a value of $P < 0.05$ was considered statistically significant. Microsoft Excel (Microsoft Office Professional Plus 2010, Redmond, WA, USA) was used to conduct inductive thematic analysis, classifying qualitative data obtained through an open-ended question into meaningful answers. The proportion of respondents reporting the most common responses was described.

Results
Demographic characteristics of the survey respondents
The survey was completed by 108 primary care clinicians. Of these, 87 were GP, 7 were GP registrars, 9 were practice nurses and 5 did not provide their level of appointment. The respondents’ practices were located in metropolitan Brisbane ($n = 68$), regional/remote Queensland ($n = 30$), locum positions or outside Queensland ($n = 5$) and five respondents did not provide their Practice post-code. A surveyor was present during administration of the survey and the participation rate was 100%. Six respondents completed less than 50% of the survey and were excluded from all further analyses. The remainder of the respondents completed >65% of the survey. The median number of different patients seen by a respondent each week was 80.

Characteristics of the patient populations
Overall, respondents estimated that $15.5 \pm 13.5\%$ of their patient population had type 2 diabetes, $19.1 \pm 13.1\%$ had dyslipidaemia or hypertriglyceridaemia, $21.7 \pm 14.4\%$ had hypertension, $28.6 \pm 17.2\%$ were overweight or obese, and $16.6 \pm 12.2\%$ consumed excess alcohol. A substantial proportion of the respondents indicated that NAFLD was not common among their patients, with $38.2\%$ estimating the prevalence to be $\leq 10\%$ (Fig. 1). There was no statistical difference in the estimated prevalence of NAFLD/NASH or metabolic co-morbidities between rural and metropolitan regions (data not presented, $P > 0.05$).

Awareness of prevalence of and factors associated with NAFLD/NASH
Overall, 51% of respondents considered the prevalence of NAFLD in the general population to be $\leq 10\%$ (Fig. 2A) and 54% of primary care clinicians considered the prevalence of NAFLD in the obese population to $\leq 50\%$ (Fig. 2B). There was no significant difference between metropolitan and rural practitioners’ responses (data not presented, $P > 0.05$).

More than 90% of respondents recognised that overweight/obesity, type 2 diabetes, metabolic syndrome and hypertriglyceridaemia were strongly associated with NAFLD. Half of the respondents (51.0%) considered that hypertension was associated with NAFLD, and most (73.5%) considered alcohol consumption to be strongly associated with NAFLD.

Figure 1 Proportion of primary care clinicians estimating different rates of non-alcoholic fatty liver disease (NAFLD) in their patient population. [10%, <10%; 10–30%; >30%].

Region of Practice
associated with NAFLD. Most respondents were aware of current recommendations for ‘safe’ alcohol consumption. Approximately, 87.3% of respondents considered that the lifetime risk of harm from alcohol-related disease is reduced by drinking ≤ 2 standard drinks per day.

Perception of morbidity/mortality associated with NAFLD

Respondents were aware that simple steatosis is associated with an increased incidence of cardiovascular disease (65.7%), and future development of type 2 diabetes (73.5%). In contrast, the relative absence of liver-related outcomes associated with simple steatosis was not as well appreciated. 61.8% of respondents considered that simple steatosis is associated with increased liver-related mortality and 47.1% considered these subjects at significantly higher risk of cirrhosis. Most respondents were aware of the increased risk of cirrhosis and liver-related mortality in subjects with NASH (71.6 and 75.5% respectively).

Perception of tests for diagnosis and risk stratification of NASH

Many primary care clinicians incorrectly felt that a diagnosis of NASH can be made using serum liver enzymes (52.9%), liver imaging (70.6%) or FibroScan (62.7%). Of concern, 24.5% of respondents felt that liver enzymes (ALT and AST) are sufficiently sensitive to detect underlying NAFLD–NASH and a further 25.5% were unsure.

The majority of respondents agreed that liver enzymes (ALT, AST) (79.4%), platelet count (67.6%), serum albumin (80.4%), prothrombin time (69.6%), NAFLD Fibrosis score (81.4%), abdominal ultrasound (77.5%) and FibroScan (71.6%) can help to identify NAFLD patients with advanced fibrosis/cirrhosis. However, most respondents were unsure whether the FIB-4 score (62.7% unsure) or ELF score (63.7% unsure) could help to identify advanced fibrosis or cirrhosis.

Although 87.3% of respondents felt that 6 monthly liver enzyme tests can help to monitor disease progression in patients with NAFLD, there was less clarity about the use of other tests. Many clinicians were unsure whether platelet count (26.5% unsure), FibroScan (36.3%), NAFLD Fibrosis score/Fib-4 test (43.1%) or the ELF test (56.9%) can help to monitor disease progression.

Assessment of clinical and referral practice

Respondents were asked whether they utilise certain tools in their clinical practice to assess their patients with NAFLD (Fig. 3). A total of 92 and 87.3% use liver enzymes and abdominal ultrasound, respectively, for NAFLD assessment. However, the majority of clinicians do not use FibroScan (80.4%). NAFLD Fibrosis score (76.5%), Fib-4 score (85.3%), AST to Platelet Ratio Index (APRI) score (78.4%) or ELF test (74.5%).

With respect to clinical management, the majority of clinicians would provide information on optimising diet and exercise (94.1%), provide a GP management plan and team care arrangements (74.5%) and refer to a dietician (90.2%). Forty-seven percent of respondents stated that they would refer a patient to a Gastroenterologist/Hepatologist if they suspect the patient has NAFLD.

Despite this, when asked how many referrals they make to Hepatology each month for an opinion regarding suspected NAFLD/NASH, 44.1% do not make any referrals and a further 44.1% make less than 1–2 referrals each month (Fig. 4). Common reasons provided for not referring patients to Hepatology included: ‘The patients do not want referral’ (18.8%), ‘There is no specific pharmacotherapy available’ (6.3%), ‘I manage them myself by optimising lifestyle’ (38.5%). ‘The waiting list is too long’ (12.5%), ‘I don’t see many patients with NAFLD/NASH’ (31.3%), ‘I do not think it is necessary’ (4.2%). Of concern, 70.6% of clinicians said they were unlikely to refer a patient to Hepatology unless liver function tests are abnormal. A total of 22 respondents volunteered additional written comments, of whom 31.8% highlighted their own lack of knowledge regarding NAFLD, for example ‘After doing this survey I realise I don’t know very much about this important topic...’.
Primary care clinicians have a key role in the initial identification and management of NAFLD and in recognising patients at risk of significant liver disease, who may require specialist referral for further evaluation. Recent clinical guidelines have emphasised the use of fibrosis algorithms or serum biomarkers rather than routine liver blood tests, to assess advanced fibrosis in people who have been diagnosed with NAFLD. The present study indicated that the majority (>85%) of primary care clinicians do not use TE, fibrosis biomarkers or algorithms in their clinical practice, to assess their patients with NAFLD. In addition, the majority of clinicians (70.6%) said they were unlikely to refer a NAFLD patient for a Hepatology opinion unless liver function tests are abnormal. These findings are concerning because liver enzyme levels do not correlate with histological findings and reliance on abnormal liver tests may fail to identify patients with significant liver disease.

Similar to our findings, a recent survey among 64 GP in The Netherlands found that serum markers/scores were never (73%) or rarely (22%) used to assess NAFLD/NASH and referral to specialist care was highly dependent on elevated liver tests. Not surprisingly, the authors found that GP were not familiar with NAFLD clinical practice guidelines prepared by the hepatology medical societies. Most of the liver-related morbidity and mortality associated with NAFLD occurs in patients with advanced fibrosis, who are at risk of developing complications of end-

**Figure 3** Proportion of primary care clinicians utilising certain tools in their clinical practice, to assess their patients with non-alcoholic fatty liver disease. Region of practice: [ ], Metropolitan; [ ], rural.

**Figure 4** Approximate number of referrals made to hepatology each month for an opinion regarding suspected non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. [ ], None; [ ], 1–2 per month; [ ], 3–5 per month.
stage liver disease and hepatocellular carcinoma. Assessment for liver fibrosis within primary care is important to determine prognosis, monitor disease progression and to decide if and when to refer to specialist care. At present, a practical approach to NAFLD diagnosis and staging in the community is recommended, using locally available tests. These include simple non-invasive fibrosis algorithms (NAFLD fibrosis and FIB-4 scores), commercial non-invasive fibrosis tests (the Enhanced Liver Fibrosis test), liver ultrasound and TE (if available). In patients with NAFLD, liver stiffness measurements (LSM) have a high negative predictive value and a modest positive predictive value for detecting advanced fibrosis. Table 1 summarises the components of locally available risk stratification tools and their interpretation.

Our findings demonstrate that many primary care clinicians underestimate the overall prevalence of NAFLD in their community. Approximately half of respondents considered the prevalence of NAFLD in the general population to be ≤10% and 38.2% considered the prevalence of NAFLD in their patient population to be ≤10%. These perceptions conflict with recent reports estimating that GP are likely to encounter more than 300 cases of NAFLD for every 1000 patients that are seen. In a recent large, population-based study from The Netherlands (n = 3041 individuals ≥45 years), 32.8% of participants had evidence of NAFLD on ultrasonography, in the absence of secondary causes of steatosis. Clinically relevant fibrosis (defined by LSM ≥ 8 kPa) was present in 8.4% of the NAFLD subgroup and in 17.2% of participants with both diabetes and steatosis. Underappreciation of the prevalence of NAFLD may contribute to many affected individuals remaining undiagnosed, in part because the condition is usually asymptomatic and associated with relatively normal or only mildly elevated liver enzyme levels.

Our findings also demonstrate lack of recognition of the clinical spectrum of NAFLD and how this is assessed. NAFLD represents a spectrum of disease from bland steatosis to the necro-inflammatory form, NASH, which is characterised by inflammation and cellular damage (hepatocyte ballooning). Although fibrosis may develop in both steatosis and NASH, fibrosis progression occurs at a more rapid rate in patients with NASH. A meta-analysis of NAFLD studies assessing paired liver biopsies found that on average, fibrosis progressed by 1 stage over 7.1 years for patients with NASH and by 1 stage over 14.3 years for patients with bland steatosis. In this survey, >50% of respondents incorrectly considered that a diagnosis of NASH could be made using serum liver enzymes, liver imaging and/or FibroScan. The diagnosis of NASH requires a liver biopsy, because clinical features, biochemical or imaging tests cannot distinguish steatohepatitis from bland steatosis, and non-invasive tests are not currently validated for this purpose. Recent data from longitudinal studies suggest that fibrosis stage, rather than the presence of NASH, is the most important histological feature associated with liver-related outcome.

**Conclusion**

Despite recognition that these patients are at risk of progressive liver disease, approximately 45% of primary care respondents correctly identified the prevalence of NAFLD in their patient population to be ≥10%. Approximately half of respondents considered the prevalence of NAFLD in their patient population to be ≤10%.

<table>
<thead>
<tr>
<th>Test/Score</th>
<th>Specific components</th>
<th>Interpretation/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>—</td>
<td>Low platelet count suggestive of advanced fibrosis</td>
</tr>
<tr>
<td>Serum albumin level</td>
<td>—</td>
<td>Late finding</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td>AST/ALT ratio</td>
<td>Low serum albumin level may be seen in advanced liver disease</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td>AST/ALT ratio</td>
<td>Late finding; not specific for chronic liver disease</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>&gt;0.8 – higher risk of advanced fibrosis</td>
</tr>
<tr>
<td>Enhanced Liver Fibrosis test</td>
<td>Commercial panel comprising tissue inhibitor of matrix metalloproteinase 1, hyaluronic acid, procollagen III amino terminal peptide</td>
<td>Manufacturer recommends a cut-off &gt;9.8 for severe fibrosis</td>
</tr>
<tr>
<td>FibroScan</td>
<td>Uses pulse-echo ultrasound</td>
<td>Provides a liver stiffness measurement (LSM) as a surrogate marker of fibrosis</td>
</tr>
<tr>
<td>FibroScan</td>
<td>Trained operator required</td>
<td>LSM &lt; 8.2 kPa – advanced fibrosis unlikely in NAFLD</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>≥1.455 – low risk for advanced fibrosis</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>&gt;0.675 – suggestive of advanced fibrosis</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>Age dependent – interpret with caution &lt;35 years or &gt;65 years.</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>High rate of intermediate scores</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>&lt; 1.3 – low risk for advanced fibrosis</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>&gt;2.67 – suggestive of advanced fibrosis</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>Age dependent – interpret with caution &lt;35 years or &gt;65 years.</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>Provides a liver stiffness measurement (LSM) as a surrogate marker of fibrosis</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>LSM &lt; 8.2 kPa – advanced fibrosis unlikely in NAFLD</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>Manufacturer recommends a cut-off &gt;9.8 for severe fibrosis</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>Age, AST, ALT, platelet count</td>
<td>Recommended by UK NICE guidelines as first-line test for advanced fibrosis in NAFLD</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; LSM, liver stiffness measurements.
care clinicians do not make any referrals to hepatology services for an opinion regarding suspected NAFLD/ NASH. This may result in many affected subjects remaining undiagnosed, consequently leading to patients presenting late with decompensated cirrhosis or hepatocellular cancer. Indeed, we have previously shown up to 46% of new referrals for NAFLD can present with advanced disease. Recognition of subjects with early or compensated cirrhosis is important, as these patients require surveillance for the development of gastroesophageal varices and hepatocellular cancer. Several respondents volunteered written comments on the questionnaire form referring to their perceived lack of knowledge regarding NAFLD. In surveys from The Netherlands18 and an urban western US population,28 84% of GP and 83% of largely primary care providers, respectively, endorsed the need for increased awareness and knowledge on NAFLD. Our Australian data in conjunction with others, support the global need for educational strategies to improve the recognition and assessment of NAFLD by primary care clinicians. Practical approaches to address this include the provision of educational workshops to increase recognition.22 Another approach would be to utilise existing models of care to improve patient management by upskilling primary care practices.29

References


20 Dyson JK, Amstee QM, McPherson S. Non-alcoholic fatty liver disease: a practical approach to diagnosis and staging. Frontline Gastroenterol 2014; 5: 211–18.


Acute oxygen therapy: an audit of prescribing and delivery practices in a tertiary hospital in Perth, Western Australia

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Key words oxygen inhalation therapy, prescription practice, inappropriate prescribing, oxygen, Western Australia.

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Abstract

Background: Oxygen is a widely used drug in the hospital setting. However, international audits suggest that oxygen administration practices are often not compliant with prescribed standards. This can place patients at risk and cause serious adverse events.

Aim: To analyse data related to recent practices of oxygen prescription and administration at Royal Perth Hospital (RPH), Western Australia. The results of this audit aim to guide further research on possible interventional studies implementing key solutions.

Methods: All patients who received care in the Acute Medical Unit at RPH between 1 September and 14 September 2015 were included in this audit. Patients who were given supplemental oxygen during their admission were selected for further review of records. Appropriate medically indicated target oxygen saturations for each patient were judged under consultation with a respiratory specialist.

Results: A total of 65 patients received oxygen supplementation within the study period: 36 of these patients (55.4%) had target oxygen saturations prescribed by doctors, and 25% of the prescribed targets were judged to be inappropriate. In total, 49 patients (75.4%) were exposed to a potential risk from oxygen therapy due to prescription error and/or delivery error. A real risk was identified in 19 patients (29.2%) as they received oxygen at levels outside their appropriate medically indicated target range.

Conclusion: The current practices of oxygen prescription and administration within RPH are suboptimal. Patients are placed at risk of oxygen toxicity due to deviation from oxygen prescription guidelines.

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Introduction

Oxygen supplementation is an essential component of the management of hypoxia. It aims to ensure that sufficient oxygen is provided at a tissue level to meet metabolic demand. However, if provided inappropriately, oxygen administration can lead to significant adverse effects. Oxygen is generally not indicated in breathless patients who do not have hypoxia, even in the setting of a cerebral vascular accident or acute coronary syndrome. Over-oxygenation can result in airway parenchymal injury, local vasoconstriction, ventilation-perfusion mismatch, adverse cardiovascular events and accentuation of pre-existing hypercapnia. The latter can lead to significant end-organ damage and carbon dioxide narcosis. Over-oxygenation can artificially increase saturation levels, masking subtle clinical deterioration and diverting focus from underlying causes of hypoxia.

A number of guidelines has been published internationally to standardise safe and effective oxygen therapy. Royal Perth Hospital (RPH), a tertiary hospital in Perth, Western Australia, is governed by the Western Australian (WA) oxygen therapy guidelines, which are similar to the British Thoracic Society guidelines. The guidelines highlight the indications for oxygen, including guidance on correct target saturation levels for different patient groups. The aim to actively wean stable patients off oxygen is emphasised through regular monitoring and titration of oxygen therapy.

The accurate completion of a dedicated oxygen prescription chart is instituted in the WA guidelines, with daily medical review of the prescription chart recommended. The RPH Oxygen Prescription chart was developed in 2012 (Fig. S1, Supporting information) following the WA guidelines. Doctors at RPH are required to use this chart to prescribe clear parameters for inpatient oxygen therapy.

Several international audits on oxygen therapy have been conducted, showing relatively widespread substandard practices, with the potential to result in significant adverse patient outcomes. In 2010, the UK National Patient Safety Agency reported 281 serious incidents related to oxygen use over 5 years, including 9 deaths and 35 contributions to death. Despite the importance of this topic, a review of literature demonstrates limited research on recent oxygen therapy practices in Australian tertiary hospitals. The aim of this audit is to create a snapshot of current practices within our institution to help guide future interventions and audits.

The Acute Medical Unit (AMU) at RPH admits all medical patients from the Emergency Department. Patient care continues under AMU if the length of stay is anticipated to be less than 72 h; otherwise, care is transferred to other hospital specialties. At the time of this study, RPH AMU comprised 43 beds, with an average length of stay for AMU patients of 1.6 days and a daily patient turnover of 72%. Due to the acuity and varied nature of patients in the AMU, together with the high patient turnover and regular involvement of different specialties, the unit is a good base for conducting research to gauge hospital-wide practices.

Methods

All patients cared for in AMU between 1 September and 14 September 2015 were selected for this audit. For each patient, notes and observation charts were reviewed. Patients who were provided supplemental oxygen at any point of their hospital stay were selected for further analysis. Those who were not administered oxygen were not included for further analysis in this audit. A questionnaire was developed to standardise data collection while reviewing all available records for these patients. Areas of focus for data collection included clinical information related to oxygen delivery and relevant patient background, particularly any history of chronic respiratory disease or smoking.

Patients’ notes were checked for the presence of filled oxygen prescription charts (Fig. S1, Supporting information) to determine the target saturation level prescribed (P). Filled charts were also examined for any errors or omissions in the eight required fields, as indicated in Figure S1 (Supporting information). If an oxygen prescription chart was not utilised, any target saturation level described by medical staff in patient notes was considered the prescribed oxygen target (P) for nurses to follow. Observation charts (Fig. 1) were assessed to determine each patient’s average oxygen saturation (S) while on oxygen supplementation. As per the observation chart, oxygen saturations were classified into three groups: > 94%, 88–92% and <88%. Non-parametric techniques were then used to determine the mean oxygen saturation obtained.

Royal Perth Hospital healthcare software (iSoft) was used to search for previous arterial or venous blood gases for each patient. A history of CO₂ retention in conjunction with a background of chronic lung disease was used to determine a predisposition to type 2 respiratory failure. These data were reviewed by a Respiratory Consultant who led the consensus on confirming this predisposition and determining the appropriate medically indicated target oxygen saturation that should have been prescribed for each patient (IP). As per WA guidelines, patients with a predisposition to type 2 respiratory failure were determined to have an ideal
medically indicated target oxygen saturation of 88–92%, whilst those without this predisposition had an ideal medically indicated target oxygen saturation of 94–98%.

The prescribed targets (P), medically indicated targets (IP) and average oxygen saturations achieved (S) were evaluated and compared to determine any potential or real risk to each patient. A potential risk was considered to be a ‘prescription error’ if prescriptions were missing (no P) or incorrect (P not equal to IP) or a ‘delivery error’ if there was inappropriate provision of oxygen (S not equal to P). Real risk to the patient was considered to have occurred when oxygen delivery (S) differed from the medically indicated target saturation for that patient (IP), resulting in either insufficient oxygenation (S < IP) or over-oxygenation (S > IP).

Results

During the study period, 327 patients were admitted to the RPH AMU; 19.9% of these patients (65) received oxygen therapy during their admission. Oxygen was often initiated in the Emergency Department prior to AMU admission and continued in AMU on transfer (44.6% of patients). The mean age of patients given oxygen was 69 years (SD = 19 yrs). Table 1 outlines other key characteristics, including risk of Type 2 respiratory failure, for the patients who received oxygen.

Of the 65 patients receiving oxygen therapy, 53.9% had a dedicated oxygen prescription chart. Two patients had target saturations documented in their medical notes without the use of a prescription chart. In total, 44.6% of patients received oxygen supplementation without any prescription. Oxygen saturations were not documented prior to oxygen supplementation in 37%.

Of the completed prescription charts, 94.3% were not filled appropriately (Fig. 2). On average, two errors/omissions were noted per prescription chart, most commonly in the field related to weaning instructions. Documentation with regards to weaning oxygen therapy occurred in only 20%.

Of those patients who had target saturations prescribed, half were in the range of ‘88–92%’, and the

Figure 1 Excerpt from RPH Inpatient observation chart showing oxygen saturation and oxygen delivery; S, Patient’s oxygen saturation while on supplementation.

Figure 2 Completion of oxygen prescription chart in patients receiving oxygen therapy (see Figure S1 (Supporting information) for fields considered mandatory): (a), No chart used; (b), chart filled, but with errors/omissions; (c), chart filled without errors.

Table 1 Characteristics of patients receiving oxygen therapy (total n = 65)

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>n (% out of patients receiving oxygen therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>40 (62.0)</td>
</tr>
<tr>
<td>Background of</td>
<td></td>
</tr>
<tr>
<td>• Chronic obstructive pulmonary disease (COPD)</td>
<td>20 (30.8)</td>
</tr>
<tr>
<td>• Tuberculosis/sarcoidosis</td>
<td>4 (6.2)</td>
</tr>
<tr>
<td>• Lung cancer</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>• Asthma</td>
<td>12 (18.5)</td>
</tr>
<tr>
<td>• Interstitial lung disease</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Background/risk of type 2 respiratory failure</td>
<td>21 (32.3)</td>
</tr>
<tr>
<td>On home oxygen prior to presentation</td>
<td>4 (6.2)</td>
</tr>
<tr>
<td>Smoking status:</td>
<td></td>
</tr>
<tr>
<td>• Not recorded</td>
<td>9 (13.9)</td>
</tr>
<tr>
<td>• Non-smokers</td>
<td>22 (39.3)</td>
</tr>
<tr>
<td>• Current smokers</td>
<td>18 (32.1)</td>
</tr>
<tr>
<td>• Ex-smokers</td>
<td>16 (28.6)</td>
</tr>
<tr>
<td>Respiratory condition as primary diagnosis in current admission</td>
<td>29 (44.6)</td>
</tr>
<tr>
<td>Purely AMU admission (no other specialty as treating team)</td>
<td>26 (40.0)</td>
</tr>
</tbody>
</table>

AMU, Acute Medical Unit.
other half were ‘>94%’. Analysis of clinical information to determine the appropriate medically indicated target (IP) for each patient identified a risk of developing Type 2 Respiratory Failure in 32.3%. Comparing prescribed target saturations (P) with medically indicated targets (IP) showed that 25% of prescriptions were inappropriate. Figure 3 illustrates the total number of prescription errors causing potential risk to patients.

Comparing patient saturations achieved during oxygen therapy (S) with prescribed targets (P) showed that 38.9% of patients received oxygen above the prescribed level (S > P). No patient had an oxygen saturation below the prescribed level (S < P). Figure 4 illustrates delivery errors causing potential risk to patients.

Of the patients, 49 (75.4%) were put at potential risk of harm from oxygen supplementation, identified as missing or inappropriate oxygen prescriptions or incorrect oxygen titration, as detailed above. In total, 19 patients (29.2%) were exposed to a real risk of complications as a result of inappropriate oxygen therapy, where oxygen saturations (S) deviated from the medically indicated target (IP): 18 patients were over-oxygenated, and 1 patient was under-oxygenated (Fig. 5).

The mean length of stay for all patients, including patients not requiring oxygen supplementation, admitted to AMU during the study period was 1.6 days. The average admission duration of patients requiring oxygen supplementation (including patients transferred to other specialties) was 6.7 days; 40% of patients on oxygen were discharged home from AMU without the transfer of care to any other specialty. The average length of stay for these patients on oxygen who were discharged home directly from AMU was 2.5 days. So, patients requiring oxygen supplementation appear to have a longer hospital stay.

Two patients were discharged home with a new prescription for home oxygen, and one was transferred to another hospital still requiring oxygen therapy. The remaining 62 patients returned to their baseline (pre-admission) oxygen status.
Results show that the prescription, administration and monitoring of acute oxygen therapy is suboptimal at our institution, with a significant proportion of patients placed at potential risk of oxygen-related adverse events. The concept of an oxygen prescription chart has been instituted in guidelines to emphasise the role of oxygen as a formally prescribed drug and to create awareness of the potential for oxygen toxicity. It is clear from the data presented that the use of oxygen prescription charts within RPH needs improvement. In total, 55% of the patients receiving oxygen therapy had prescribed target saturations, and only 3.1% of them had fully completed oxygen prescription charts.

A 2005 audit showed that, at North Shore Hospital, New Zealand, 2% of patients receiving oxygen had it adequately prescribed ‘with respect to guidelines’, while a 2013 audit in Waikato Hospital, New Zealand showed a 51.7% correct prescription rate, which was defined as ‘containing flow rate, device and appropriate oxygen saturation aims, considering the patients’ medical history and risk of hypercapnia’. The BTS has conducted audits of oxygen-prescribing practices within the National Health Service (NHS) since the implementation of the 2008 guidelines. The most recently available data from a 2013 audit demonstrated that 55% of patients using oxygen had some form of written order, an improvement from only 32% in 2008. Therefore, international data suggest that the standards of practice at RPH are generally similar to those in other countries. There is a pressing need to audit regularly and improve oxygen administration practices in hospitals worldwide.

The low portion of correctly filled prescription charts found in this study may be due to a variety of factors, including the number of fields required to be completed, time constraints and inadequate education relating to correct prescribing practices. It was found that many doctors completed the flow rate, delivery system, application and target saturation fields on the prescription chart but did not complete the weaning instructions. The prescription chart appears to be unnecessarily complicated; thus, it is our recommendation that the prescription chart be simplified for ease of use. The field for weaning instructions may be omitted from revised prescription charts as administration should be titrated based on oxygen requirements.

The guidelines for appropriate oxygen administration advise targeting oxygen saturations of 94–98% for patients who are hypoxaemic, with the exception of patients who are at risk of type 2 respiratory failure and certain types of poisoning. Patients at risk include those with prior hypercapnic respiratory failure, known severe chronic obstructive pulmonary disease, morbid obesity, chest deformities or neuromuscular disorders. In the acutely unwell patient in the non-emergency setting, blood gases should be performed to assess the risk of hypercapnic respiratory failure to aid oxygen titration accordingly. This is particularly true for patients with COPD given that a proportion of these will not be at risk of type 2 respiratory failure. This is relevant to our study population, where we found that doctors tended to be biased towards under-oxygenation when prescribing.

Two-thirds of the prescription errors were due to target saturations prescribed below appropriate medically indicated targets. This is likely due to insufficient research into patients’ backgrounds before prescribing, resulting in an inaccurate estimation of oxygen requirements. In practical terms, this could be due to the time constraints faced by prescribers working in a busy department combined with insufficient stress on the importance of accurate oxygen prescription. AMU’s nature as a unit dependent on shift work and rapid turnover makes it
hard for doctors to maintain continuity of care and obtain a deep knowledge of each patient’s background.

Although prescriptions often leaned towards under-oxygenation, the administration of oxygen leaned towards oversupply. Oxygen is often not down-titrated or weaned to meet prescribed targets, resulting in over-oxygenation. This may be due to insufficient focus on the prescription chart target while filling the observation chart. As there is no marker on the observation chart to alert staff to a filled prescription chart, it is likely that this is easily overlooked. The counterbalancing nature of these errors explains why not all the patients found to be at potential risk from oxygen therapy in our study (75.4%) were at real risk.

The real risk to patients in this study was still significant; 18 patients (27.7%) were at risk of oxygen toxicity, and 1 patient was under-oxygenated and at risk of hypoxia. This risk profile illustrates a significant non-compliance with oxygen administration standards.

This study highlights several areas requiring improvement, mostly surrounding inadequate prescription and inaccurate titration of oxygen. As oxygen was frequently continued without reassessment after being initiated prior to admission, any quality improvement programmes should also include the Emergency Department. Previous studies have shown that interventions focusing on visual reminders of oxygen guidelines, redesign of inpatient observation charts and nurse-initiated oxygen prescription education have resulted in significant improvements in oxygen therapy practices. These encouraging results demonstrate the positive potential impact of instituting oxygen-related interventions, which can be quantified in future re-audits.

There are clearly areas of limitation within this study. Data collection was retrospective in nature and relied on accurate documentation by staff in patient notes and observation charts. Lapses in documentation resulted in loss of data. Logistical problems related to file retrieval forced the exclusion of four study patients who may have received oxygen. Patients who were not administered oxygen were not further assessed to determine their oxygen requirements. The magnitude of variations between prescribed, delivered and ideal oxygen saturations was not analysed in this study.

Data collection was mainly based in one medical ward and restricted to a short study period. However, as almost all medical patients are admitted through the AMU, we feel the data provide valid information on acute oxygen therapy practices at the hospital and are likely to be reproducible in other Australian hospitals that use a similar process of admission. It is hoped that these data provide a useful basis for further research and intervention related to oxygen delivery practices in Australian hospitals.

Conclusion

The current practices of oxygen prescription and administration within RPH Acute Medical Unit are suboptimal. Patients are placed at risk of oxygen toxicity due to deviation from oxygen prescription guidelines. Based on the data from this study, recommendations have been made to the executive team at Royal Perth Hospital to improve oxygen therapy practices, including simplification of the prescription chart, in order to reduce patients’ risk of oxygen-related adverse events.

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References

Supporting Information

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

Figure S1. RPH oxygen prescription chart; P, Prescribed target saturation level; 1–8, Fields required for a fully complete chart.

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Incidence of in-hospital and post-discharge diagnosed hospital-associated venous thromboembolism using linked administrative data

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Key words
venous thromboembolism, incidence, diagnosis, risk factors, complications.

Abstract

Background: Hospital-associated venous thromboembolism (HA-VTE) is a serious adverse event, preventable with appropriate care during and post-admission. Accurate measurement of in-hospital and post-discharge incidences is essential for implementation and evaluation of prevention strategies and monitoring.

Aims: To estimate in-hospital and post-discharge diagnosed VTE, trends and risk factors.

Methods: This was a population-based study in New South Wales, Australia, using linked hospital admission and emergency department data for 2010–2013 of adult patients with a minimum stay of 48 h. HA-VTE were diagnosed in-hospital or post-discharge (within 90 days). Multi-level modelling schemes produced adjusted rates and ratios for patient, admission and hospital-related characteristics.

Results: From 1 865 059 admissions, the HA-VTE incidence rate was 9.7 per 1000 admissions; 71% were diagnosed post-discharge, and 4.3% died with a greater risk for VTE diagnosed in hospital compared to post-discharge (8.4% vs 2.6%, P < 0.001). Compared with surgical patients, medical patients developed fewer HA-VTE (IRR = 0.60, 95% CI: 0.58–0.63) but were more likely to be diagnosed post-discharge (OR = 2.19; 95% CI: 2.00–2.40). HA-VTE increased 6.5% over the period, driven by the 44% increase in in-hospital diagnoses and not by the 9% decrease in post-discharge diagnoses.

Conclusions: HA-VTE is a continuing burden, and diagnosis after recent hospital discharge is notably high. Incidence varies across patients and facilities, highlighting the need for individual VTE risk assessment. Inclusive measures and routine monitoring of HA-VTE incidence and mortality are essential for implementing best practice and assessing effectiveness of prevention strategies.

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Conflict of interest: None.
Introduction

Venous thromboembolism (VTE) is a major, potentially preventable cause of morbidity and mortality.\textsuperscript{1} On a cost-per-case basis, VTE is the second ranked health condition in Australia, but including the cost of premature mortality elevates it to first place.\textsuperscript{2} Hospital admission is a major risk factor for VTE and accounts for almost 50% of the attributable risk.\textsuperscript{3} Many predisposing factors, including prolonged immobilisation, malignancy, major surgery, multiple trauma and chronic heart failure,\textsuperscript{4} commonly occur among hospital patients. Not all VTE associated with hospitalisation either occur or are diagnosed during the hospital stay;\textsuperscript{5,9} and consequently, hospital-associated VTE (HA-VTE) underreporting is common.\textsuperscript{10} VTE risk persists after surgery and beyond discharge of medical patients, with most events developing within 90 days.\textsuperscript{11} The term HA-VTE encompasses VTE acquired and diagnosed during the index admission or following discharge,\textsuperscript{12,13} reflecting this association between current or recent hospitalisation and the development of VTE. Data on readmission rates are also lacking.\textsuperscript{19} Thus, HA-VTE rates calculated only on VTE cases diagnosed during a hospital stay may underestimate the true prevalence, and burden, of HA-VTE.\textsuperscript{10,13–15} Enhanced monitoring and reporting of VTE incidents, together with awareness of its preventable nature, are key to improving the uptake of VTE risk assessment and prophylaxis.\textsuperscript{10,15}

Compared to overseas studies,\textsuperscript{7,9,14,16,17} few Australian studies have examined the incidence of HA-VTE, and most have relied on inpatient data.\textsuperscript{2,13,15,18} This study supplemented inpatient data with emergency department (ED) presentations across New South Wales (NSW) facilities to estimate more accurately the incidence of HA-VTE in NSW, including VTE diagnosed during the index admission and after discharge. Factors associated with the increased likelihood of a post-discharge diagnosis and the time of VTE diagnosis were also assessed.

Methods

Data source

Two data sources capture all admissions to NSW hospitals and presentations to contributing public ED in NSW for persons 18 years or over who were discharged between 1 July 2010 and 30 June 2014 (2010–2013 financial years). Linked records from the Admitted Patients Data Collection (APDC; 11 354 936 records) and Emergency Department Data Collection (EDDC; 9 273 285 records) were obtained from the NSW Admitted Patient, Emergency Department Attendance and Deaths Register, established under the public health and disease registers provisions of the NSW Public Health Act 2010 and maintained by the NSW Ministry of Health. Record linkage was carried out by The Centre for Health Record Linkage (CHeReL). Use of the data for this study was approved by the data provider. The APDC collects information for all admitted patient services in NSW hospitals. Principal diagnosis and comorbidities are coded using the ICD-10, Australian Modification (ICD-10-AM).\textsuperscript{19} The accompanying ‘Condition Onset Flag’ variable indicates whether each condition arose during the episode of care or was present on admission.\textsuperscript{20} The EDDC collects information about presentations to contributing NSW public ED. ED diagnosis may be coded using either ICD-10-AM, ICD-9-CM or Systematised Nomenclature of Medicine-Clinical Terms (SNOMED-CT).\textsuperscript{21}

VTE identification

VTE was defined by the ICD-10-AM codes for pulmonary embolism (PE) – I26.0, I26.8, I26.9, O88.2 – and deep vein thrombosis (DVT) – I80.1, I80.2, I80.3, I80.8, I80.9, I82.2, I82.8, I82.9, O22.3 and O87.1 – based on recognised quality and safety indicators.\textsuperscript{22,23} Corresponding ICD-9-CM and SNOMED-CT codes were determined using mapping tables provided by the Australian Consortium for Classification Development\textsuperscript{24} and the National eHealth Transition Authority (personal communication).

We identified HA-VTE and examined its association with an index admission, that is, an admission to an NSW acute public hospital (n = 82), with a minimum length of stay (LOS) of 48 h (Fig. 1). HA-VTE with condition onset and diagnosis during the index admission were classified as in-hospital diagnosed VTE (IH-VTE). HA-VTE present on admission or ED presentation to any NSW public or private hospital within 90 days\textsuperscript{11,13} of an index admission were classified as post-discharge diagnosed VTE (PD-VTE). Index admission details of these VTE were analysed. Any VTE diagnosed within 90 days of a previously diagnosed VTE (capturing readmissions, transfers, care type changes) were excluded. Isolated HA-VTE was thus identified and differentiated from community-acquired VTE (VTE present on admission, no hospital admission within the previous 90 days\textsuperscript{13} with minimum 48 h LOS). We reported on public hospital incidence only due to lower data availability and quality in private hospitals.\textsuperscript{25}

For VTE unclassified due to missing condition onset data, logistic models to predict onset status were developed based on patient and admission characteristics from complete data. Public and private hospitals were modelled separately. Models with minimum Akaike Information Criterion\textsuperscript{26} values and maximum area under a receiver operating characteristic curve\textsuperscript{27} (0.89 and 0.98
with 11 and 7 predictors for public and private hospitals, respectively) predicted the onset status of 3824 VTE (7.6% of all isolated VTE) and subsequently identified 411 IH-VTE (10.7%), 1440 PD-VTE (37.7%) and 1973 community-acquired VTE (51.6%).

We examined data for 3 months before and after our study period to resolve time-censoring effects. Discharge status (alive/dead) at the last VTE-related hospitalisation of each isolated VTE determined case fatality. Cause of death information was not available.

**Description of covariates**

Patient characteristics included gender, age and country of birth. Admission characteristics included admission urgency, admission type based on The Australian Classification of Health Interventions\textsuperscript{28} procedure codes, surgery type, the Charlson Comorbidity Index (derived from ICD-10-AM codes for the principal diagnosis and comorbidities as defined by Quan et al.),\textsuperscript{29,30} major principal diagnosis disease groups based on the Charlson Comorbidity Index categories among VTE cases, LOS and year of separation (grouped by financial year, reported as year at 1 July). Hospital characteristics consisted of health district location and peer group. Peer groups comprised hospitals of a similar type and size.\textsuperscript{31}

**Statistical analysis**

Analyses were based on the index admission. Mixed modelling schemes were used to derive adjusted rates for outcomes and ratios for all patient, admission and hospital covariates while controlling for hospital clustering effects.

Negative binomial mixed models were employed for HA-VTE and associated case fatality rates. A logistic mixed model assessed the likelihood of in-hospital versus post-discharge diagnosed HA-VTE. Yearly adjusted incidence and fatality rates were derived by multiplying yearly adjusted rate ratios and the crude rates observed in the reference year (2010). IH-VTE and PD-VTE annual adjusted trends were obtained using an odds-to-rate ratio conversion method.\textsuperscript{32}

Data preparation was conducted using SAS Enterprise Guide V.6.1\textsuperscript{33} through SAPHaRI\textsuperscript{34} and analyses were performed using R package V.3.1.2.\textsuperscript{35}

**Results**

**Hospital-associated VTE**

Of the 1 865 059 (13.3% of all APDC records) eligible admissions between 1 July 2010 and 30 June 2014, with a median LOS of 5 days (1st and 3rd quartiles: 3 and 9 days, respectively), 18 171 isolated HA-VTE were identified, yielding an incidence rate of 9.7 per 1000 admissions (median LOS = 8 days, quartiles: 5 and 16 days). Patients were diagnosed with one (n = 16 407) or multiple isolated HA-VTE; 834 patients contributed 1764 cases (9.7% of all HA-VTE). DVT is more common (11 378; 62.6%) than PE. There were 7693 HA-VTE identified and excluded as repeat presentations of an HA-VTE diagnosed within the previous 90 days. An additional 32 058 diagnosed VTE were classified as community acquired (Fig. 1).

The majority of HA-VTE were diagnosed post-discharge (12 837; 70.6%). In-hospital diagnosed HA-VTE had a longer median LOS (18 days, quartiles: 11 and 33) than PD-VTE (6 days, quartiles: 4 and 11). Excluding PD-VTE involving a hospital transfer or care type change (n = 2907), median time between index admission discharge and subsequent diagnosis admission was 17 days (quartiles: 6 and 40 days).

The risk of HA-VTE is shown in Table S1 (Supporting information). Males had 9% (IRR = 0.91) lower risk of HA-VTE than females; risk increased with age. Asian-born patients had 36% less risk of developing an HA-VTE than patients born in Australia or New Zealand.

Non-emergency admissions had 17% less risk of HA-VTE than emergency admissions. Medical and obstetric admissions were associated with markedly lower rates of HA-VTE compared to surgical admissions (40% and 77% lower risk respectively). Risk varied according to surgery type: compared to cholecystectomy, patients undergoing orthopaedic procedures had 1.79–3.6 times the risk of HA-VTE. Patients with cancer were 1.5 times as likely to develop HA-VTE as patients with vascular disease. Conversely, patients with cardiac or chronic pulmonary disease had 17% and 14% lower risk respectively. Higher Charlson Comorbidity Index scores and longer hospital LOS were associated with increased risk of HA-VTE. Patients with a Charlson score of 5 or more were 1.6 times as likely to develop HA-VTE as patients scoring 0 or 1. A hospital stay of 10 or more days increased the risk of HA-VTE by 136% compared to patients with maximum LOS of 4 days. Large principal referral hospitals and hospitals in metropolitan areas had a higher likelihood of HA-VTE than smaller hospitals and those located in rural areas.

**Case fatality**

There were 775 in-hospital deaths of patients with HA-VTE (case fatality 4.3%) during the study period; 413 (53.3%) were PE, and 447 (57.7%) occurred within the index admission. Case fatality was higher for PE than...
DVT (6.1% vs 3.2%, \( P < 0.001 \)) and for in-hospital compared to PD-VTE (8.4% vs 2.6%, \( P < 0.001 \)).

**Time trends**

The adjusted incidence rate of HA-VTE increased by 11% from 9.2 in 2010 to 10.2 in 2012, with a non-significant decline to 9.8 in 2013 (6.5% increase from 2010) (Fig. 2). The adjusted rate for IH-VTE also increased (44%) throughout the study period. Most of the increase (20%) occurred between 2012 and 2013, mirrored by a marked drop (1 per 1000 patients; 14%) in the adjusted rate of PD-VTE, resulting in a 9% overall decline (Fig. 2). PE as a proportion of VTE decreased.
from 39.3% to 35.7% across the study period (Table S1, Supporting information). Adjusted hospital case fatality remained stable at 4.0%.

**In-hospital versus PD-VTE**

Patient, case mix and hospital factors affected the odds of a post-discharge diagnosis (Table S1, Supporting information). The likelihood of PD-VTE increased with age, being a medical patient (OR = 2.19), coronary artery bypass graft (OR = 2.34) or hip replacement surgery (OR = 1.61), cancer (OR = 1.79) and chronic pulmonary disease (OR = 2.07) and admission to smaller district hospitals (OR = 2.32) or hospitals in rural and regional areas (OR = 1.60). Planned admissions (OR = 0.86), knee replacement surgery (OR = 0.56), mid-range Charlson scores (OR = 0.86), increased hospital LOS (OR = 0.05) and more recent year of admission (OR = 0.69) were associated with reduced odds of PD-VTE.

**Discussion**

This analysis of almost two million admissions to NSW acute public hospitals over 4 years identified 18 171 isolated HA-VTE events, an incidence rate of 9.7 per 1000 admissions. HA-VTE incidence amongst surgical admissions was almost twice that of medical admissions and varied across surgical types and diagnoses groups. Less than one-third of HA-VTE was diagnosed during the index admission. The overall HA-VTE case fatality rate was 4.3% and was more likely for patients with in-hospital compared to PD-VTE (8.4% vs 2.6%).

Our findings of a persistent risk of VTE following discharge and HA-VTE most commonly diagnosed post-discharge (59% of surgical, 83% of medical, 71% of all patients) are consistent with previous research from Australia and overseas. Our higher proportions of HA-VTE diagnosed within 3 months of a previous admission (compared to 54% of medical patients and 53% of all patients) may reflect patient and methodological differences. Differences in measuring time to diagnosis and case mix may have contributed to our shorter delay to PD-VTE identification (17 days) compared to some (51 days) but not all (16 days) reports. Capturing VTE diagnosed post-discharge expanded our study population to include patients with an increased likelihood of later diagnosis, particularly medical, compared to surgical, admissions and patients attending smaller hospitals, compared to principal referral hospitals. Consequently, our estimates of HA-VTE within the Australian context are more accurate than previous reports, which – based only on in-hospital diagnosed VTE – yielded an incidence rate of 11.5 per 1000 admissions, and update other results, which are
more than 10 years out of date (2–3 per 1000 admissions). The marked difference in the incidence rates for medical patients (8.1 vs 4.5), compared to the smaller difference for surgical patients (15.5 vs 12.9), between our and previous studies highlights the impact of including post-discharge VTE. The high incidence of VTE diagnosed after hospital discharge is cause for concern. While not all HA-VTE will become clinically apparent during an admission, especially with the trend towards shortened LOS, our results support the urgent call for more individualised VTE risk assessment, appropriate thromboprophylaxis and an extension of thromboprophylaxis into the post-discharge period.

There was no evidence of a decrease in HA-VTE during the study period despite national- and state-wide guidelines and policy directives to increase awareness and prevention of HA-VTE through routine risk assessment and appropriate prophylaxis. More recently, NSW Health’s Clinical Excellence Commission established a state-wide VTE Prevention Program, including updated strategies, resources, support and advice, to assist clinicians and facilities to implement VTE risk assessment and prophylaxis into the clinical workflow and ultimately reduce HA-VTE in NSW hospitals. This study provides a baseline for programme evaluation against which anticipated reductions in incidence can be measured.

Insufficient dosage or duration of prophylaxis may increase rates of both IH-VTE and PD-VTE. Quantifying the risk of post-discharge diagnosis reveals those patient, admission and hospital factors where greater vigilance and attention to assessing patient risk and prescribing appropriate thromboprophylaxis may be warranted. The traditional view that VTE is primarily a complication of surgery has been discounted by research documenting the high incidence of VTE amongst medical patients and the underutilisation of appropriate prophylactic modalities in both the hospital and post-discharge setting amongst this group. The elevated odds of PD-VTE amongst medical, compared to surgical, patients in our study suggests that risk stratification for PD-VTE and extended prophylaxis among medical patients is advantageous. However, medications are not recorded in the administrative data analysed in our study, precluding examination of prophylaxis and its influence on HA-VTE. Investigation into the appropriate duration of prophylaxis is warranted.

Encouragingly, the adjusted incidence rate for post-discharge VTE decreased in the final year of the study, with a corresponding increase in VTE identified during the index admission. Increased awareness of VTE as a preventable adverse event may have had an initial effect in increasing the number of VTE identified while the patient was still in hospital. The crude trend towards a decreasing proportion of PE observed in our study may imply earlier diagnosis. Awareness is integral to behaviour change and adoption of guidelines but needs to be translated into action. The NSW Clinical Excellence Commission’s initiatives are aimed at facilitating behaviour change. Reassessment of our measures and process parameters following full implementation of these initiatives will reveal whether the desired outcomes have been achieved.

Our higher HA-VTE incidence in large principal referral hospitals may relate to the severity and complexity of patient caseload, which was not fully captured by our case mix. In contrast, an inability to detect asymptomatic VTE in smaller district hospitals (mostly located in rural areas) due to limited health resources, in combination with the characteristic optimism and stoicism of rural Australians, which contributes to delayed help-seeking behaviour, may have contributed to the elevated risk of a PD-VTE diagnosis and resulted in a larger proportion of PE. PE, as indicated by higher case fatalities in smaller hospitals, is associated with poorer outcomes. Clinical practice guidelines promote evidence-based practice aimed at overcoming unwarranted variation and improving patient outcomes, but their success is dependent on implementation and uptake.

Post-discharge VTE can be difficult to measure because patients may not re-present to the original hospital; may be treated solely as an outpatient, including by their local doctor or may not seek medical attention. Many studies investigating PD-VTE have restricted their sample to a specific group of patients or used classification methods to enhance onset data completeness, and longitudinal follow up of patients enabled identification of HA-VTE versus community-acquired VTE or consecutive re-presentations of the same VTE. Identifying isolated VTE events avoided double counting repeated VTE presentations. Accordingly, our rates of both hospital-associated and post-discharge VTE have greater validity and more accurately depict the extent of this problem, filling the gap in prevalence estimates based on administrative datasets. Although supported by literature, our decision to include all VTE diagnosed within 90 days of discharge as PD-VTE may have missed some late onset HA-VTE but also potentially underestimated PD-VTE by incorrectly including some community-acquired VTE.
Reporting on HA-VTE in private settings provides additional insight, although lower quality in their administrative data requires more caution.\textsuperscript{23} Our post-discharge diagnosis rate, based on hospital data, is likely a conservative estimate as we were unable to identify patients diagnosed and treated solely at outpatient clinics or by their local doctor or presenting to non-contributing ED. Current methodologies used to record this information in NSW are disparate and are not amenable to linkage with hospital data,\textsuperscript{13} making it difficult to accrue these data. In the United Kingdom, linked primary care and hospital administrative data identified an additional 38\% of post-surgical VTE.\textsuperscript{16} Differences in healthcare systems and study methodologies prevent applying this rate directly to our results but suggest a noteworthy underestimation of HA-VTE. The inability to capture the small proportion of patients who may have re-presented to hospitals in states bordering NSW also potentially underestimates the post-discharge rate. Case mix variables, such as smoking, obesity, history of VTE, risk assessment and prophylaxis, were not included in our modelling.

Future analyses incorporating such details might provide insight into influences on the onset and diagnosis of HA-VTE.

**Conclusion**

HA-VTE incidence increased over time and varied across patients and facilities. Recognition of variation in risk advances efforts to improve targeted risk assessment and diagnosis. The significantly elevated incidence of post-discharge HA-VTE suggests the need for improved prevention strategies. Adopting inclusive measures and routine monitoring and reporting of HA-VTE incidence and associated mortality are essential to the implementation of best practice and assessment of effectiveness.

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**References**


32 Grant RL. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ* 2014; **348**: i7450.


Off-label use of rituximab in autoimmune disease in the Top End of the Northern Territory, 2008–2016

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Key words
rituximab, autoimmune diseases, systemic lupus erythematosus, off-label, Aboriginal Australian.

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Abstract
Background: Rituximab, an anti-CD20 B-cell depleting monoclonal antibody, is increasingly prescribed off-label for a range of autoimmune diseases. There has not previously been an audit of off-label rituximab use in the Northern Territory, where the majority of patients are Aboriginal.

Aims: To evaluate retrospectively off-label rituximab use in autoimmune diseases in the Top End of the Northern Territory.

Methods: We performed a retrospective audit of 8 years of off-label rituximab use at the Royal Darwin Hospital, the sole tertiary referral centre for the Darwin, Katherine and East Arnhem regions. Electronic and paper records were reviewed for demographic information, diagnosis/indication for rituximab, doses, previous/concomitant immunosuppression, clinical outcomes and specific adverse events.

Results: Rituximab was prescribed off-label to 66 patients for 24 autoimmune diseases. The majority of patients (62.1%) were Aboriginal and 60.6% female. The most common indications were refractory/relapsing disease despite standard therapies (68.7%) or severe disease with rituximab incorporated into an induction immunosuppressive regimen (19.4%). Systemic lupus erythematosus was the underlying diagnosis in 28.8% of cases. A clinically significant response was demonstrated in 74.2% of cases overall. There were 18 clinically significant infections; however, 13 were in patients receiving concurrent immunosuppressive therapy. There was a total of nine deaths from any cause.

Conclusion: Rituximab has been used off-label for a range of autoimmune diseases in this population with a high proportion of Aboriginal patients successfully and safely in the majority of cases.

Introduction

Rituximab is a monoclonal antibody directed at the CD20 surface antigen expressed on precursor and mature B cells, but not plasma cells. Rituximab depletes B cells from the peripheral circulation through a variety of mechanisms, including antibody-mediated and complement-dependent cytotoxicity and B-cell apoptosis.1 Rituximab was initially developed for the treatment of non-Hodgkin lymphoma and was first made available on the Australian Pharmaceutical Beneﬁts Scheme (PBS) for this indication in 2003.2 It is also licensed for use in CD20+ chronic lymphocytic leukaemia.

Rituximab has increasingly been utilised in the treatment of autoimmune diseases. A number of proposed mechanisms for its efficacy in this setting relate to the disruption of B- and T-cell interactions thought important in

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generating autoimmunity.\textsuperscript{3,4} In 2007, rituximab gained PBS listing for use in severe rheumatoid arthritis in combination with methotrexate \textsuperscript{5} and in early 2016 for induction of remission in granulomatosis with polyangiitis and microscopic polyangiitis.\textsuperscript{6} These are the only indications other than B-cell neoplasms for which rituximab is licensed by the Therapeutic Goods Administration.

Off-label prescribing of rituximab is expanding to a wide range of autoimmune diseases, in most cases without high-quality evidence to support its use.\textsuperscript{7} A prospective data collection in Australian public hospitals in 2012 recorded 364 instances of off-label rituximab use prescribed for 63 different conditions over a 6-month period.\textsuperscript{8} Forty percent of the indications for which it was prescribed had level 4 evidence of benefit (case series, case–control or historically controlled studies).\textsuperscript{9} This 2012 study did not include data from the Northern Territory.

The Northern Territory population has the youngest median age (32 years) and the highest proportion of Aboriginal Australians (30\%) of all states and territories.\textsuperscript{9} The majority of the population lives in the Top End region, which has only one tertiary referral hospital with a catchment area of over 500 000 km\textsuperscript{2}.\textsuperscript{10} Aboriginal Australians are overrepresented in the Northern Territory public health system accounting for 70\% of hospital patients in 2013–2014.\textsuperscript{11} The burden of infectious disease is high with a fourfold greater incidence of sepsis amongst Aboriginal people compared with the non-Aboriginal population living in the Top End.\textsuperscript{10} Over 80\% of the Northern Territory’s Aboriginal population lives in an area classified as remote or very remote.\textsuperscript{12} These demographics and the distances over which healthcare must be delivered create unique challenges for the Northern Territory health system.

This audit provides a descriptive retrospective analysis of 8 years of off-label use of rituximab for autoimmune disease in the Top End of the Northern Territory, including evaluation of its efficacy and safety. It adds to the Australian national data on off-label rituximab use and provides the first substantial information on its use in Aboriginal Australians.

**Methods**

The Human Research Ethics Committee (HREC) of the Northern Territory Department of Health and Menzies School of Health Research granted ethical approval for this audit, which met National Health and Medical Research Council criteria for a quality assurance activity and was deemed negligible/low risk. Patient information was deidentified in line with HREC requirements.

Cases of off-label rituximab use between April 2008 and August 2016 were identified from a database kept by the Royal Darwin Hospital pharmacy containing all cases of off-label rituximab prescribed for patients residing in the Darwin, Katherine and East Arnhem health regions. Demographic information, diagnosis/indication for rituximab, doses given, previous and concomitant immunosuppressants, clinical outcomes and specific adverse events (see below) were recorded by searching electronic and paper medical records for each patient, up to 1 November 2016. Cases where rituximab was given for a haematological malignancy or rheumatoid arthritis were excluded. Anti-neutrophil cytoplasmic antibody-associated vasculitis-associated vasculitis was included; however, all cases either predated PBS approval or did not meet approval criteria.

Rituximab was prescribed for a heterogeneous array of autoimmune diseases and validated disease-specific measures of response not always documented, hence the following definitions of response were devised:

1 Clinically significant response (CSR): Patient demonstrated clinical benefit from rituximab in terms of improvement in organ function or symptoms, or halting of disease progression or prevention of further relapses, such that
   \begin{itemize}
     \item \textbf{a} the patient did not require any further immunosuppression or
     \item \textbf{b} the initial clinical benefit of rituximab was maintained with stable immunosuppressive therapy, including not more than 10 mg prednisolone/day or
     \item \textbf{c} further doses of rituximab were given to treat disease relapses or to maintain the initial clinical benefit.
   \end{itemize}

2 No response (NR): Patient had no clear clinical benefit from rituximab in terms of symptomatic improvement or organ function as reflected by the applicable disease activity tests, requiring the commencement of a different immunosuppressive agent in an attempt to gain disease control.

In addition, five subcategories of CSR were derived based on duration of response, the number of courses of rituximab required, need for other immunosuppressive agents and ultimate clinical outcome (Table 1).

We sought the following specific adverse events:
\begin{itemize}
  \item \textsuperscript{(i)} infusion reactions, \textsuperscript{(ii)} anaphylaxis or hypersensitivity reactions, \textsuperscript{(iii)} infections requiring inpatient treatment occurring up to 12 months since the last administered dose of rituximab, \textsuperscript{(iv)} hepatitis B reactivation, \textsuperscript{(v)} progressive multifocal leukoencephalopathy, \textsuperscript{(vi)} new diagnoses of malignancy, \textsuperscript{(vii)} hypogammaglobulinaemia and \textsuperscript{(viii)} all-cause mortality.
\end{itemize}
Results

Sixty-six patients met inclusion criteria (Figure 1, Supporting Information Table S1). One of the 66 patients responded to rituximab for systemic lupus erythematosus (SLE)-associated pancytopenia initially, but not at time of relapse 2 years later, and therefore contributed a CSR followed by NR (discussed further below). The average time from first dose of rituximab to the end of the study period was 3 years and 4 months. A total of nine patients died and three patients were lost to follow-up before the end of the study period.

Patient demographics

The median age of the patients at time of first rituximab administration was 38.5 (range 13–79) years and 40 (60.6%) were female. Of the females, 31 (77.5%) were Aboriginal, with a median age of 26 (range 13–60) years compared with a median age of 53 (range 25–73) years in the non-Aboriginal female group. Of the 26 males, 10 (38.5%) were Aboriginal, with a median age of 47 (range 20–60) years compared with a median of 55 (range 22–79) years in the non-Aboriginal male group. The majority of Aboriginal patients lived in remote communities (87.8%) compared with 1.5% (one patient) from the non-Aboriginal group.

Indications and efficacy

In over two-thirds of episodes (68.7%), rituximab was given for disease refractory to or relapsing on other immunosuppressive therapies. In 19.4% of cases, rituximab was used in conjunction with other immunosuppressants (intravenous immunoglobulin and high-dose corticosteroids in the majority) as induction therapy in an acute illness deemed severe and life-threatening. In 11.9% of cases, rituximab was prescribed because of side effects from standard therapies or variable adherence to prescribed immunosuppressive medication.

Rituximab was given for 24 different diagnoses. Table 2 summarises the number of cases and responses for each diagnosis. The most common diagnoses were thrombotic thrombocytopenic purpura (TTP) (CSR in seven of seven cases), inflammatory myopathy (CSR in six of seven cases), immune thrombocytopenic purpura (ITP) (CSR in two of seven cases), anti-neutrophil cytoplasmic antibody-associated vasculitis-associated vasculitis (CSR in five of five cases), autoimmune encephalopathy (CSR in four of four cases), SLE – not otherwise subcategorised (CSR in four of eight cases) and lupus nephritis (CSR in three of four cases). A total of 19 patients had an underlying diagnosis of SLE having met Systemic Lupus International Collaborating Clinics classification criteria. CSR was demonstrated in 14 of the 19 SLE patients (73.7%).

Table S1 provides further details about the clinical scenario and outcome for each patient. Overall, a clinically significant response to rituximab was demonstrated in 49 of 66 patients (74.2%).

In three cases of ITP, assessment of response was contested by splenectomy within a month of rituximab administration. These cases have been included in the NR category.

Adverse events

Table 3 summarises adverse events. There were 18 cases of infection requiring inpatient treatment. There were no cases of hepatitis B reactivation. Hepatitis B serology had been documented prior to rituximab in each case and any patient with chronic hepatitis B infection commenced on antiviral therapy. There was only one case of hypogammaglobulinaemia identified in a patient who was on concurrent chemotherapy for multiple myeloma. However, testing of serum immunoglobulins was inconsistent.

There were nine deaths during the study period. Further details of each death are given in Table S1. Of note, a patient with ITP died of multi-organ failure attributed to disseminated cytomegalovirus infection 2 weeks following rituximab, however, this patient had also received both high-dose dexamethasone and methylprednisolone in the weeks prior to her death.

Table 1 Categories of clinically significant response (CSR) to rituximab

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>No. cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSR 1</td>
<td>No ongoing immunosuppression required following one or two courses of rituximab. Steroids weaned completely. ≥2 years since last rituximab</td>
<td>15</td>
</tr>
<tr>
<td>CSR 2</td>
<td>No ongoing immunosuppression required following one or two courses of rituximab. Steroids weaned completely. &lt;2 years since last rituximab</td>
<td>8</td>
</tr>
<tr>
<td>CSR 3</td>
<td>Relapsing disease responsive to further rituximab, or rituximab used as maintenance agent to prevent relapses</td>
<td>14</td>
</tr>
<tr>
<td>CSR 4</td>
<td>Remission induced or significant improvement with rituximab, remains stable on another immunosuppressive agent (not more than 10 mg/day prednisolone)</td>
<td>5</td>
</tr>
<tr>
<td>CSR 5</td>
<td>Clinically significant response to rituximab, but died or lost to follow-up before end of study period</td>
<td>7</td>
</tr>
</tbody>
</table>
Also of note, a patient who had received rituximab 2 years prior for SLE-related pancytopenia with subsequent normalisation of cell counts and no ongoing requirement for immunosuppression, represented with pancytopenia (including severe thrombocytopenia), but did not respond to rituximab on this occasion. Three months later he presented with a spontaneous intracranial haemorrhage and received methylprednisolone, intravenous immunoglobulin and vincristine. He also underwent splenectomy, but died a short time later in the community (cause of death not known).

Discussion

This retrospective audit adds to our current knowledge of the frequency and outcome of off-label use of rituximab for autoimmune diseases in Australia. It is the first audit of rituximab use presented from the Northern Territory and the largest documented cohort of Aboriginal Australians to have received rituximab.

The disproportionately high number of young Aboriginal females in this audit (46.3% of the total, median age 26 years) reflects the increased prevalence and severity of autoimmune disease generally amongst this demographic. The prevalence of SLE in Aboriginal people living in the Darwin, Katherine and East Arnhem regions of the Northern Territory was estimated 20 years ago to be twice that of the non-Aboriginal Australian population. Several other studies focusing on remote Australian populations have also identified a higher prevalence of SLE in Aboriginal compared with non-Aboriginal people living in the same regions. One of the authors (PB) collected a database of SLE patients from 2009 to 2015, and estimated prevalence of SLE amongst Top End Aboriginal Australians to be 140 per 100 000 people.

Although the number of cases per diagnosis was small, overall there was evidence of a clinically significant response to rituximab in close to three quarters of cases. TTP had an excellent response rate (seven of seven cases). In each case, TTP disease was either refractory, relapsing or deemed severe. Evidence from observational and uncontrolled studies supports the use of rituximab in TTP in patients with suboptimal response to standard therapy.

SLE was the underlying diagnosis in a significant proportion of patients in this audit (28.8%), with three of four cases of lupus nephritis and 11 of 15 cases of SLE – other manifestations, demonstrating CSR to rituximab. Two young SLE patients who did not respond had...
advanced and likely irreversible end-organ damage before receiving rituximab as 'last hope' therapy. Otherwise, the apparent effectiveness of rituximab in SLE in this demographic may support the hypothesis of a B-cell-dependent phenotype.19 The role of rituximab in lupus remains controversial. Two randomised clinical trials failed to demonstrate a benefit of adding rituximab to standard therapies in patients with either renal20 or non-renal lupus, however, this contrasts with the results of numerous preceding uncontrolled studies.21 Several of these studies examined the use of rituximab in patients with lupus nephritis who had failed to achieve remission from standard therapies, and supported a role for this agent in refractory disease.22 The majority of the cases described in this audit reflect this practice of prescribing rituximab in SLE resistant to standard immunosuppression. In other cases, rituximab was prescribed when standard immunosuppression presented too great a risk for infection in patients remote from acute medical care, such as in the case of a patient with lupus nephritis who required aeromedical evacuation back to Darwin due to respiratory sepsis following his first dose of cyclophosphamide.

Interestingly, two patients with pulmonary arterial hypertension in the setting of SLE showed dramatic reversal of pulmonary artery pressures after rituximab. In the first case, a female patient received two courses of rituximab 1 year apart for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) on a background of SLE with class V lupus nephropathy. Her estimated pulmonary artery systolic pressure fell from >80 mmHg prior to rituximab to 43 mmHg on transthoracic echo 15 months later.

**Table 2** Summary of diagnoses and responses to rituximab

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. cases</th>
<th>CSR</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired haemophilia A</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Acquired von Willebrand factor deficiency</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ANCA-associated vasculitis</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Autoimmune encephalopathy</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Autoimmune haemolytic anaemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Catastrophic antiphospholipid syndrome†</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Chronic seronegative polyarthritis</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CIDP†</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hep C assoc. mixed cryoglobulinaemia</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Inflammatory myopathy</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>ITP‡</td>
<td>7</td>
<td>2</td>
<td>5‡</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Membrano-proliferative glomerulonephritis</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Recurrent parotitis</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SLE – not otherwise subcategorised</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Transverse myelitis†</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TTP‡</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reaction</td>
<td>5</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>3</td>
</tr>
<tr>
<td>Hypersensitivity reaction (rash)</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>18</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>11</td>
</tr>
<tr>
<td>Skin/soft tissue</td>
<td>3</td>
</tr>
<tr>
<td>Meningitis – Listeria monocytogenes</td>
<td>1</td>
</tr>
<tr>
<td>Gastroenteritis – Shigella spp.</td>
<td>1</td>
</tr>
<tr>
<td>Disseminated CMV infection</td>
<td>1</td>
</tr>
<tr>
<td>Dental abscess (1)</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis B reactivation</td>
<td>0</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>0</td>
</tr>
<tr>
<td>New diagnosis of malignancy</td>
<td>5</td>
</tr>
<tr>
<td>Acute myeloid leukaemia (secondary)</td>
<td>1</td>
</tr>
<tr>
<td>Thymoma</td>
<td>1</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
</tr>
<tr>
<td>Squamous cell carcinoma, skin</td>
<td>1</td>
</tr>
<tr>
<td>Small cell carcinoma of lung</td>
<td>1</td>
</tr>
<tr>
<td>Hypogammaglobulinaemia</td>
<td>1</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>9</td>
</tr>
<tr>
<td>Disseminated CMV infection</td>
<td>1</td>
</tr>
<tr>
<td>Spontaneous intracranial haemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>in the setting of ITP</td>
<td></td>
</tr>
<tr>
<td>Haemorrhage secondary to assault in</td>
<td>1</td>
</tr>
<tr>
<td>the setting of SLE-related hepatic failure with coagulopathy</td>
<td></td>
</tr>
<tr>
<td>Haemolytic-uraemic syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Gallstone pancreatitis</td>
<td>1</td>
</tr>
<tr>
<td>Secondary acute myeloid leukaemia</td>
<td>1</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>1</td>
</tr>
<tr>
<td>Multi-organ failure presumed secondary</td>
<td>1</td>
</tr>
<tr>
<td>to sepsis on background of SLE</td>
<td></td>
</tr>
<tr>
<td>Circumstances not known</td>
<td>1</td>
</tr>
</tbody>
</table>

†A number of patients in these categories had known SLE.
‡Assessment of response in three cases of ITP confounded by splenectomy; these have been included in NR category. ANCA, anti-neutrophil cytoplasmic antibody-associated vasculitis; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; CMV, cytomegalovirus; ITP, immune thrombocytopenic purpura; SLE, systemic lupus erythematosus.

**Table 3** Adverse events following rituximab

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This audit also included a number of cases of rituximab use in autoimmune disease primarily affecting the central nervous system, with demonstrated response in all nine cases (neuromyelitis optica, transverse myelitis, CIDP, autoimmune encephalopathy). A recently published systematic review and meta-analysis of the use of rituximab in neuromyelitis optica spectrum disorders demonstrated a reduction in frequency of relapses and neurological disability, although there were no randomised trials available for inclusion.24 Success with rituximab in CIDP has been documented in a handful of case reports and small case series.25–30 Level IV evidence also exists for rituximab mainly as a second-line treatment in refractory autoimmune encephalopathy.31–33

Another group identified in this audit as having responded well to rituximab was inflammatory myopathies, comprising four cases of polymyositis, two cases where myositis was not able to be subclassified and one case of statin-induced myopathy. Only the latter did not respond (noting that anti-HMG-CoA reductase antibodies were not tested), with all other cases achieving a clinically significant response in terms of improvement in weakness with restoration of function, and return of creatinine kinase to normal range in most cases. Evidence for the benefit of rituximab in dermatomyositis and polymyositis refractory to conventional therapy comes from small case series34,35 and one randomised trial involving 195 paediatric and adult patients, all with disease refractory to glucocorticoids plus at least one other agent.36

Depletion of circulating B cells generally begins within days of rituximab administration and B-cell recovery takes 6–12 months in the majority of patients, though there is significant individual variability and longer repletion times of over 2 years have been documented.1 The relationship between B-cell recovery and disease relapse is variable, and in a subset of responders rituximab produces a more enduring state of remission despite B-cell recovery.3 In 15 of the 49 cases (30.6%) of CSR in this audit, response was achieved with the use of either one or two courses of rituximab, such that no further immunosuppression was required during the study period (and for a period of at least 2 years) (Table 1). Several patients had notably long periods of clinical remission still enduring at the end of the study period, including two cases of acquired haemophilia A (5 and 7 years) and four cases of TTP (5 years in two cases, 8 years in two cases). Data on CD19+ B-cell recovery, particularly in relation to disease relapse or ongoing remission, were mostly not available. Where CD19+ B-cell recovery was documented, it was difficult to assess disease activity at the same point in time for that patient.

Within the limits of a retrospective audit, this report also demonstrates the apparent safety of rituximab. Although there were 18 documented infections requiring inpatient treatment, in 13 of these cases the patient was on concurrent immunosuppression (>10 mg prednisolone/day in four cases; mycophenolate or azathioprine ± prednisolone 5 mg/day in five cases; prednisolone 5 mg/day in three cases; cytotoxic chemotherapy in one case). The majority of these infections were of the respiratory tract and treated successfully with standard empiric antibiotic therapy. Notably, one patient who was not on other concurrent immunosuppression presented with Listeria monocytogenes meningitis 1 month following rituximab. Another patient died of disseminated cytomegalovirus infection (see Adverse Events section above).

The clinical benefit of rituximab documented in this audit should also be supported economically. Although rituximab is costly (approximately $2000 per 500 mg), this expense would be offset by a number of benefits, including its apparent safety as an immunosuppressant in a demographic with a high prevalence of infection; supplanting variable medication adherence and its long-lived clinical efficacy. It was not in the scope of this audit to compare the rituximab-treated cohort of patients with either a contemporary or historical conventional immunosuppression control group. Nonetheless, each of the benefits attributed to rituximab here would be expected to contribute an economic advantage through reduced hospital presentations for both the primary indication and infectious complications of immunosuppression.

The main limitations of our study are its retrospective, uncontrolled nature and the inconsistent documentation of objective disease activity measures from which to draw conclusions about response to treatment. The importance of clinical governance and accountability in health care is gaining recognition world-wide. Most major hospitals in Australia have therapeutics committees tasked with providing clinical governance over special-case expenditure. This was the finding of O’Connor and Liddle in their survey of off-label rituximab use in Australian public hospitals, with the majority of requests approved through a local therapeutics committee (78%).9 Such committees formalise review of evidence supporting off-label use of specific therapeutics and promote good clinical practice by requiring clinicians to document patient consent and specify how outcomes will be assessed and recorded. Clinical governance over special-case expenditure on rituximab in the Top End of the Northern Territory was not formalised during the study period.

Conclusion

The gold standard of double-blind randomised placebo controlled trials to determine efficacy and safety are
unlikely to occur for medications used in rare diseases, and even less likely to include the demographic subject of this audit. Off-label prescribing of rituximab in autoimmune disease is increasing, particularly when standard immunosuppression has failed or is poorly tolerated. This audit of off-label rituximab use in the Top End of the Northern Territory demonstrated that rituximab is increasingly utilised in this population effectively and safely in the majority of cases. Formal clinical governance structures, such as a therapeutics committee would facilitate future auditing, research and quality assurance.

Acknowledgements

We would like to acknowledge the following clinicians for clarification of certain patient case details, advice on specific clinical measures of outcome following rituximab therapy or contribution in the early stages of assembling this audit (in alphabetical order): Dr Jim Burrow (neurologist, Royal Darwin Hospital (RDH)), Dr Pasqualina Coffey (public health registrar, Northern Territory Centre for Disease Control), Ms Genevieve Francois (pharmacist, Katherine Hospital), Ms Bianca Heron (pharmacist, RDH), Dr Akash Kalro (haematologist, RDH), Dr Akshay Kulkarni (medical registrar, RDH), Dr Cheng Lu (medical registrar, RDH), Dr William Majoni (nephrologist, RDH), Dr Babu Philip (immunologist, RDH), Ms Tristen Pogue (pharmacist, RDH), Dr Simon Quilty (general physician, Katherine Hospital), Dr Madhivanan Sundaram (nephrologist, RDH), Dr Ferenc Szabo (haematologist, RDH) and Ms Joanna Wallace (pharmacist, RDH).

References

19. Vincent FB, Bourke P, Morand EF, Mackay F, Bossingham D. Focus on


## Supporting Information

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

**Table S1.** Details of patients, clinical scenario and outcomes.
Characteristics of adrenal incidentalomas in a New Zealand centre

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Abstract

Background: Management of adrenal incidentalomas (AI) is becoming more conservative, based on international data showing a low incidence of functional or malignant lesions. The clinical characteristics of AI in New Zealand are unknown. Therefore, whether the AI guidelines apply to the New Zealand population is also unknown.

Aims: To investigate the clinical characteristics of patients with AI presenting to a tertiary-care centre in New Zealand.

Method: This study prospectively evaluated consecutive patients aged 18 or older with AI, 1 cm or larger, diagnosed in Canterbury, New Zealand. A standardised nurse-led dedicated AI clinic was used, including clinical assessment, hormonal evaluation and imaging.

Results: From January 2010 to April 2016, 306 patients were referred to the AI clinic, 228 met the inclusion criteria. Most of those excluded were not true AI, due to imaging performed for known or suspected non-adrenal malignancy. The most common reason for imaging was abdominal pain (46%). Most cases were benign (96.5%) and 88.6% of all cases were non-functional. Of the functioning tumours (26 patients), 18 had subclinical Cushing syndrome, four had late-onset congenital adrenal hyperplasia, two had phaeochromocytoma and one had primary hyperaldosteronism. Three patients had primary adrenal cancer, one of whom was secreting excess cortisol. One adrenal metastasis was diagnosed.

Conclusion: This study found a similar prevalence of functional and malignant AI as international centres, although mild cortisol excess and primary aldosteronism may be under-represented. Therefore, the conservative approach to management of AI recommended in current guidelines is likely to be applicable to New Zealand population.

Introduction

Adrenal incidentalomas (AI) are defined as adrenal masses that are discovered unexpectedly on imaging performed for an unrelated reason.1,2 Adrenal masses are common and the reported prevalence has been increasing due to the continued advances in imaging technology and widespread use of imaging in clinical practice.2

The main clinical concerns in AI are the risk of malignancy and presence of hormone overproduction. However most AI are non-functional, benign cortical adenomas that require no treatment.1,3

Based on international studies, the prevalence of AI is reported as 3–10% and 93–98% of AI are benign.1,2,4 About 5–15% of the benign adenomas are functional tumours which produce excess hormones.4

Previous guidelines have involved significant investigation and follow up of AI with associated costs.2,5 In view of this more recent literature, guidelines have evolved to a more conservative approach to management of AI, particularly regarding follow up if the AI is thought to be benign and non-functioning at presentation.4

It is unclear if the guidelines are applicable to local patients as the clinical characteristics of AI in the New Zealand population may be different from international centres.

This paper aims to investigate the clinical characteristics of AI patients who presented to a tertiary-care centre in New Zealand.

Key words
adrenal tumour, adrenal cancer, incidentaloma.

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Methods

Patients

This study prospectively evaluated consecutive patients aged 18 or older with AI, 1 cm or larger, discovered on imaging in the Canterbury region of New Zealand between January 2010 and April 2016. If the AI was discovered by abdominal ultrasound, it was confirmed by computed tomography (CT). The patients were assessed in a dedicated nurse-led AI clinic following a standardised protocol (in Supporting Information Appendix S1).

Patients were excluded if imaging was initiated due to signs or symptoms of adrenal disease (e.g. severe hypertension, hypokalaemia, Cushingoid features), known malignancy under surveillance in the last 5 years (other than cured skin basal cell carcinoma or squamous cell carcinoma), metastatic malignancy found on referring CT scan, incomplete hormonal evaluation or hormonal results that could not be interpreted due to patients being on long-term, high-dose prednisone.

If there were abnormal findings on hormonal testing or imaging, the patients were seen by an endocrinologist and diagnosis was based on further investigations and clinical review. Adrenalectomy was offered to patients with clinically significant hormonal hypersecretion or radiographic features suspicious of malignancy.

CT findings

Adrenal tumours characterised by attenuation value of ≤10 Hounsfield units (HU) or rapid contrast medium washout (absolute contrast medium washout of more than 60%, 10 min after administration of contrast) were considered benign adrenocortical adenomas. If there were multiple adrenal nodules, CT characteristics of each nodule were assessed. Dedicated adrenal CT scan was performed in those whose initial scan had only contrast-enhanced images. The CT findings were reported by radiologists from one District Health Board who are expert at abdominal imaging.

Data collection

Data were prospectively collected on patients assessed in the AI clinic, including medical history, blood pressure and anthropometric data. All patients had a nurse-led clinical examination for signs of Cushing syndrome, including proximal muscle weakness, pathologic striae, bruising and skin thickness.

Biochemical analysis

Investigations included plasma sodium and potassium, random plasma glucose, renal function, HbA1c, plasma metanephrine and normetanephrine and 24 h urine collection for cortisol, metanephrine and normetanephrine. Where possible, blood tests were performed seated and in the morning. Due to geographical issues (the population catchment area is over 45,000 km), there were occasional patients who had their tests performed in the afternoon. Urine testing was chosen in preference to a low dose overnight 1 mg-dexamethasone suppression test partly due to geographical reasons as this allowed all tests to be done with one clinic visit and the subsequent urine collection was then handed to a laboratory near the patient’s home address.

Plasma testosterone and DHEA-S were assayed in female patients with hirsutism. If the CT showed bilateral adrenal masses, the patient was evaluated for late-onset congenital adrenal hyperplasia (CAH) (Synacthen test for 17-OH progesterone), Serum testosterone (female reference range 0.3–2.7 nmol/L), DHEA-sulphate (reference range 0.5–12.0 μmol/L), 17-OH progesterone (reference range post Synacthen test <30 nmol/L) were measured by in-house ELISA method (Canterbury Health Laboratory).6-9

Autonomous cortisol secretion was considered excluded if the 24 h urine cortisol excretion was normal. If the 24 h urinary cortisol excretion (reference range: 100–400 nmol) was elevated, a 1 mg dexamethasone suppression test (reference range < 50 nmol/L) was performed. Serum cortisol and 24 h urine cortisol excretion were measured by in-house ELISA method (Canterbury Health Laboratory).9,10 Patients with both an elevated 24 h urine cortisol and post 1 mg-dexamethasone cortisol underwent clinical review by an Endocrinologist. Patients were diagnosed with subclinical Cushing syndrome (SCS), as per the commonly used definition in the literature at the time, that is, the absence of clinical signs of cortisol excess plus at least two biochemical abnormalities of the hypothalamic–pituitary–adrenal axis.11-13

Plasma aldosterone and renin were measured if the patient was hypertensive (defined as the use of antihypertensive drugs, or blood pressure > 140/90 mmHg) or was hypokalaemic. Anti-hypertensive medications were not changed prior to the screening test. Prior to July 2014, plasma aldosterone was assessed by direct displacement radioimmunoassay (units ng/L) and plasma renin measured in an antibody trapping assay (units nmol/L/h).14,15 After July 2014, plasma aldosterone and renin were measured by chemiluminescence provided by Immunodiagnostics Systems, Specialty Immunoassay

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System (IDS-iSYS). Where possible, blood tests were performed seated and in the morning, however due to geographical issues, there were occasional patients who had tests performed in the afternoon. A raised aldosterone to renin ratio (ARR) (>800 prior to July 2014 or >30 with the newer assay) was considered suggestive of primary hyperaldosteronism, and those patients went on to review by an Endocrinologist and, where appropriate, confirmatory testing with recumbent saline suppression test was performed. An aldosterone level of >210 pmol/L post saline infusion was considered as diagnostic of primary hyperaldosteronism. Other centres may use a lower cut-off level of aldosterone for saline suppression test. Recent primary aldosteronism guidelines suggest a level of 190 pmol/L, which would have a higher sensitivity, but a lower specificity.\textsuperscript{16}

Plasma metanephrine (reference range <500 pmol/L) and normetanephrine (reference range <900 pmol/L) and 24 h urine metanephrine (reference range <1.5 μmol/24 h) and normetanephrine (reference range < 2.9 μmol/24 h) were measured by liquid chromatography (LC)–mass spectrometry detection.\textsuperscript{17}

### Results

From January 2010 to April 2016, 306 patients with an adrenal mass were referred to the AI clinic, of whom 228 patients met the inclusion criteria. Seventy-eight patients were excluded – 14 due to incomplete biochemical testing (Table 1), 15 as their adrenal lesion was smaller than 1 cm; 46 as they were not true incidentalomas (36 due to CT scans being performed for known malignancy or metastatic malignancy found on referring CT scan, five due to hypertension under investigation, five did not have adrenal mass). Other reasons for exclusion included three patients on prednisone.

Table 2 shows the clinical characteristics of patients with AI. The most common reason for abdominal imaging was abdominal pain (46%) followed by detection of an abnormality found on CT chest (11.8%). The majority were female (59.6%). The mean age was 60.6 years, range 20–86 years. Most of the AI were on the left (55.3%), 30.7% on the right and 14% were bilateral. The mean diameter was 21 mm, with median diameter 18 mm, range 10–82 mm.

Table 3 and Figure 1 show the final diagnosis of the AI. Most cases were benign as defined by CT imaging criteria (96.5%). Twenty-six patients had functioning tumours, of whom 18 had subclinical Cushing syndrome, four had late onset CAH, two had phaeochromocytoma and one had primary hyperaldosteronism. There were no cases of Cushing syndrome.

Primary adrenal cancer was diagnosed in three patients, one of which was functional with cortisol excess and the other two were non-secretory. One adrenal metastasis was found in a patient having been treated surgically and considered cured for Merkel cell carcinoma 6 years earlier.

Three out of 18 patients with SCS underwent surgery. Fifteen patients with SCS were managed conservatively, three of whom were felt not to be surgical candidates. The other patients either had no associated medical problem or they were able to be managed medically.
Plasma aldosterone and renin were assessed in 152 patients (those with BP < 140/90 at assessment, or those on anti-hypertensive medication), of whom 89 patients were on interfering medications, such as angiotensin converting enzyme-inhibitors, angiotensin II receptor blockers diuretics and three patients were taking spironolactone. One patient was diagnosed with primary hyperaldosteronism as she was on candesartan 32 mg daily. She did not have confirmatory testing as she was aged 86 years and surgery was not thought to be appropriate. She responded well to spironolactone. Four other patients had raised ARR ratios, two of whom were unfit for further investigations, one was a false positive and the last patient declined further testing. There were no patients with positive confirmatory saline suppression test.

**Discussion**

This study describes the baseline characteristics of 228 patients assessed in a dedicated AI clinic in Canterbury, New Zealand, over a 6-year period.

Of the study cohort, 190 patients (83.3%) were diagnosed with benign non-functioning adrenal adenomas, 18 patients (7.5%) with SCS, 4 patients (1.7%) with late onset CAH, 2 patients (0.9%) with phaeochromocytoma and 1 patient (0.4%) with primary hyperaldosteronism. Four patients (1.7%) had a malignant condition, three of which were primary adrenal carcinoma. The prevalence rates for these conditions are similar to a review of nine higher quality studies, with the possible exception of phaeochromocytomas which we found in 0.9% of patients, compared to 0–5.3%, mean 3.1%, median 3.0%, found in these other studies.4

The mean diameter of AI in this study was 21 mm, which is smaller than in a review of the nine higher quality studies (e.g. mean 32 mm).4 This may be due to increased use of imaging technology leading to more AI being discovered at a smaller size, improved resolution of newer imaging technology and/or greater awareness of reporting radiologists for adrenal pathology.

The prevalence of patients diagnosed with primary hyperaldosteronism in this study was 0.4%, which may be falsely low due to our exclusion criteria and the lack of cessation of all anti-hypertensive medication. However, the prevalence in this study was similar to that found in those studies that likely best reflect the true prevalence of hyperaldosteronism in AI (e.g. range 0–1.8%, mean 0.6%, median 0%).4

There was a very low detection rate of adrenal metastasis, only one patient, which likely relates to the predetermined protocol, focusing on true AI and excluding patients with a history of cancer in the last 5 years or those diagnosed with metastatic cancer on the referring CT scan.

New European guidelines for the assessment of AI were published after this study was commenced. The European Society of Endocrinology clinical practice guideline no longer uses the term ‘subclinical Cushing syndrome’ and instead classifies patients as having ‘possible autonomous cortisol secretion’ or ‘autonomous cortisol secretion’ based on the results of the 1 mg-dexamethasone suppression test.1 As a result, our centre now uses the 1 mg-dexamethasone suppression test as the initial assessment of cortisol autonomy in AI patients.

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**Table 3** Diagnosis of adrenal incidentalomas

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign non-functioning adenoma</td>
<td>190 (83.3)</td>
</tr>
<tr>
<td>SCS</td>
<td>18 (7.9)</td>
</tr>
<tr>
<td>Late onset CAH</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Indeterminate†</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Adrenocortical carcinoma‡</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Ganglioneuroma§</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Phaeochromocytoma‡</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Myelolipoma§</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Primary hyperaldosteronism</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Lymphangioma‡</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Merkel cell metastasis†</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

†Patients with indeterminate CT adrenal scan either had interval follow up CT scan that showed no change in size of adrenal lesion, or had declined surgical intervention. ‡All patients with adrenocortical carcinoma, melanoma, melanoma, melanoma, melanoma and melanoma underwent surgical excision and diagnosis was confirmed on histology. One of two patients with myelolipoma underwent surgery which confirmed the diagnosis and the other patient was diagnosed based on scan characteristics. CAH, congenital adrenal hyperplasia; CT, computed tomography; SCS, subclinical Cushing syndrome.
despite the geographical challenges. It is possible that by using urinary free cortisol instead of 1 mg-dexamethasone suppression test, we may have missed some patients with possible autonomous cortisol secretion.

This study does not provide any data on whether initially non-functional benign adenomas gain functionality over time or whether patients with AI should have follow-up imaging. The European Society of Endocrinology clinical practice guideline has suggested routine follow-up of patients with non-functional adenomas smaller than 4 cm is not indicated.1

Of note, all patients in this study were diagnosed at a single, tertiary-care medical centre in New Zealand, raising the possibility that the data may not be representative of the wider New Zealand population. According to the 2013 census data, 8.1% of the Canterbury population identifies as Maori, compared to 14.9% of the overall New Zealand population.17 In addition, 86.9% of people in Canterbury belong to the European ethnic group, compared with 74% for New Zealand.18 The study however offers the advantage of being the largest source of AI data for New Zealand population.

Conclusion

The characteristics of AI in Canterbury, New Zealand, are similar to international centres, although mild cortisol excess and primary aldosteronism may have been under-represented in this study. This study provides support that adapting the recent changes to management guidelines would likely provide similar outcomes to international centres, at least for the Canterbury population. A follow up study of these patients with AI to assess outcomes further is ongoing.

Acknowledgements

We acknowledge the work of our Endocrine nurses, especially Ms Janet Gilbert (Department of Endocrinology, Christchurch Hospital), in the acquisition of data for this study.

References

4 Cawood TJ, Hunt PJ, O’Shea D, Cole D, Soule S. Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant; time for a rethink? Eur J Endocrinol 2009; 161: 513–27.
United we stand, divided we conquer: pilot study of multidisciplinary General Medicine Heart Failure Care Program

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Abstract

Background: Heart failure care and education require a multifaceted approach to ensure appropriate transition from inpatient to outpatient care.

Aims: To explore the feasibility of a multidisciplinary heart failure care model, General Medicine Heart Failure Care Program (GM-HFCP), within a General Medical Unit (GMU).

Methods: Prospective non-randomised before-and-after observational quality improvement intervention over a 6-month period was conducted. All consecutive patients admitted to GMU at Alfred Hospital, Melbourne with a diagnosis of acute decompensated heart failure were included. Main outcome measures included changes in rates of pharmacologic prescription, non-pharmacologic ward-based management, patient education and action plan provision after intervention.

Results: In total, 108 patients were included (median age 84 (inter-quartile range 80–89) years, 47(44%) females). Significant improvements were noted in non-pharmacologic management for patient education regarding fluid restriction (12–30%, P = 0.04), weight monitoring (10–28%, P = 0.03), heart failure action plan on discharge (4–28%, P = 0.002) and salt restriction (6–32%, P = 0.002). The rates of prescription of heart failure medications remained similar between the pre- and post-implementation periods, particularly in patients with reduced ejection fraction by ‘appropriateness of prescription’ criteria. There were no differences in inpatient mortality or 30-day readmission rates in both groups.

Conclusions: This prospective observational study demonstrated that it is possible to share the roles of a heart failure nurse amongst members of the multidisciplinary team, with similar rates of delivery of pharmacologic and non-pharmacologic management aspects. However, further innovative improvements are needed to address certain aspects of heart failure care.
to address all recommended components of heart failure care.

We hypothesise that heart failure management can be effectively shared amongst members of multidisciplinary teams within General Medicine (e.g. medical, nursing and pharmacy), each taking ownership in addressing specific pharmacologic and non-pharmacologic aspects. The aim of this quality improvement project was to explore the feasibility of such shared responsibility approach in improving education and management of inpatients with heart failure, in lieu of a dedicated heart failure nurse, using process measures as outcomes.

**Methods**

**Setting**

This was a single-centre prospective non-randomised before-and-after observational quality improvement intervention, evaluating changes in process measures after implementation of a general medicine heart failure care programme at The Alfred hospital, Melbourne, Australia. The hospital is a 350-bed university affiliated quaternary hospital, with the General Medical Unit (GMU) consisting of five medical inpatient teams having approximate bed occupancy of 20–30% of total acute hospital beds.

**Study population**

All consecutive patients admitted to GMU with a clinical diagnosis of acute decompensated heart failure (ADHF) were included in this study. All eligible patients were identified from the daily admission lists by the study investigators (OI and VN). The pre-implementation (baseline) and post-implementation (intervention) audit periods were over 8 weeks each between 21 March 2016 and 15 May 2016, and between 1 August 2016 and 26 September 2016 respectively. Patients were excluded from the final comparative analyses if they received end-of-life care during the hospital admission. Approval to conduct this study was granted by the institutional Human Research Ethics Committee (approval number: Alfred 182/16).

**Intervention**

A multidisciplinary programme, named General Medicine Heart Failure Care Program (GM-HFCP), was designed specifically for general medicine inpatients admitted with ADHF. GM-HFCP was designed by a steering committee within the GMU as a collaborative quality improvement project between general medicine physicians, a heart failure physician, heart failure nurse, general medical nurses and pharmacists. The individual components of GM-HFCP and task assignments were outlined in Table 1. The programme was developed over a 6-week period from mid-May 2016 (at the end of baseline audit period) to early July 2016.

Programme implementation period was over 2 weeks from 18 July 2016 to 31 July 2016. This involved providing education to members of the GMU team including general medicine doctors (interns and registrars), nursing and pharmacists on heart failure management as per Australian National Heart Foundation Heart Failure guidelines and task assignment for GM-HFCP. Implementation was conducted by the study investigators, and a one-off reinforcement session was also provided on 15 August 2016, the first 2 weeks into the post-implementation period. A heart failure management pack was developed, which included patient information, daily weight monitoring chart and heart failure action plan based on the guidelines, to be provided to patients during admission and upon discharge.

**Data collection**

Demographic and clinical details were extracted from medical records. Data on non-pharmacologic and pharmacologic management, and provision of heart failure education and/or action plan were collected using a case report form at two-time points: 1 day after admission and at discharge. Non-pharmacologic ward-based management data were collected including daily weight recordings, daily fluid balance recordings, daily renal function and electrolyte (UEC) monitoring, orthostatic blood pressure (BP) monitoring, salt restriction status and whether patient education and action plan were provided and documented. Pharmacologic management data that were collected included use of beta-blockers, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker (ACEi or ARB), frusemide,
spironolactone and digoxin. If these medications were not prescribed, reasons were recorded.

Definitions

Left ventricular ejection fraction (LVEF) of ≥50% was defined as heart failure with preserved ejection fraction (HFPEF) and LVEF of <50% was defined as heart failure with reduced ejection fraction (HFREF), in keeping with American Heart Association (AHA) classification.6 Last available transthoracic echocardiogram result on electronic medical records was used to determine heart failure classification.

‘Appropriate prescription/non-prescription of medications’ was defined as patients being on appropriate classes of medications (ACEi/ARB, beta-blockers and aldosterone antagonists) for correct indication (i.e. HFREF), and if not prescribed, with appropriate reasons or contraindication documented in notes/results (e.g. acute kidney injury, hyperkalaemia or side effects) or observation charts (e.g. bradycardia, hypotension or orthostatic intolerance).

Outcome measures

Outcome measures included changes in rates of pharmacologic prescription, adherence to non-pharmacologic ward-based management components and patient education and action plan provision between pre-implementation and post-implementation periods. Appropriate use of pharmacologic management in HFREF, inpatient mortality rates and 30-day readmission rates were also measured.

Statistical analysis

All categorical variables were expressed as counts and proportions. Numerical variables were assessed for normality of distribution, and expressed as median and interquartile ranges. Comparisons between pre- and post-implementation process measures were performed using bivariate models employing Mann–Whitney U-tests, Chi-squared and Fisher exact tests. A two-tailed P-value of <0.05 was taken as a statistically significant result.

Results

A total of 108 patients with ADHF was included over the entire study period (52 during pre-implementation and 56 during post-implementation periods). The median age of patients was 84 (80–89) years and 47 (44%) were female (Table 2). Nine (8%) patients received end-of-life care during acute admission (Table 2) and their results were censored from comparative analyses.

Comparison of clinical characteristics between the patients in two study periods is summarised in Table 2. Outcomes

After GM-HFCP implementation, there were statistically significant improvements in non-pharmacologic management especially patient education regarding fluid restriction, salt restriction, weight monitoring and provision of heart failure action plan on discharge (Table 3). Improvements were also noted in daily weight and fluid
balance documentations and orthostatic blood pressure measurements, although not statistically significant.

The overall rates of medication prescription on discharge also improved modestly after GM-HFCP implementation, particularly ‘appropriate use’ of beta blockers and ACEi/ARB in patients with HFREF ($P > 0.05$ for all variables) (Table 3). There was no difference in inpatient mortality or 30-day readmission rates between both groups ($n = 24; 12, 25\%$ vs 12, 24\% in each period, $P = 1.0$).

### Discussion

This pilot project showed that it is possible to share the responsibilities of a heart failure nurse amongst individual members of the multidisciplinary care teams within general medicine to address specific management aspects of heart failure care in a decentralised but efficient and effective manner. Overall, we found improvements in multiple aspects of patient care between pre- and post-implementation periods, lending support to this model of care.

In patients who have been hospitalised with ADHF, specialist heart failure nurse input has been shown to be associated with better health outcomes.\(^2\)\(^-\)\(^5\) However, there is often no dedicated heart failure nurse in GMUs to address and reinforce all management aspects, potentially disadvantaging these patients. Other studies utilising similar multidisciplinary strategies to ours have shown comparable improvements, in terms of patient education, medication management, nutritional guidance and adherence to cardiac rehabilitation.\(^7\)\(^,\)\(^8\) Indeed, education interventions, regardless of delivery by a dedicated heart failure nurse or by multidisciplinary teams, have been shown to improve heart failure knowledge, quality of life, enhance self-care behaviours and reduce readmission rates.\(^2\)\(^-\)\(^9\) Taken together, these studies and

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**Table 3** Non-pharmacologic management, patient education and pharmacologic management results of pre- and post-implementation periods

<table>
<thead>
<tr>
<th>Non-pharmacologic management</th>
<th>Pre-implementation ($n = 49$)</th>
<th>Post-implementation ($n = 50$)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily weight documentation, n (%)</td>
<td>42 (85)</td>
<td>45 (90)</td>
<td>0.55</td>
</tr>
<tr>
<td>Daily fluid balance chart, n (%)</td>
<td>46 (93)</td>
<td>47 (94)</td>
<td>1.00</td>
</tr>
<tr>
<td>Daily UEC checks, n (%)</td>
<td>42 (85)</td>
<td>46 (92)</td>
<td>0.35</td>
</tr>
<tr>
<td>Orthostatic BP ordered, n (%)</td>
<td>3 (6)</td>
<td>8 (16)</td>
<td>0.19</td>
</tr>
<tr>
<td>Orthostatic BP checked, n (%)</td>
<td>3 (6)</td>
<td>8 (16)</td>
<td>0.19</td>
</tr>
<tr>
<td>Salt restriction ordered, n (%)</td>
<td>3 (6)</td>
<td>16 (32)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Patient education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid restriction, n (%)</td>
<td>6 (12)</td>
<td>15 (30)</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight monitoring, n (%)</td>
<td>5 (10)</td>
<td>14 (28)</td>
<td>0.03</td>
</tr>
<tr>
<td>Action plan given on discharge, n (%)</td>
<td>2 (4)</td>
<td>14 (28)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Pharmacologic management – Overall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers, n (%)</td>
<td>25 (51)</td>
<td>33 (66)</td>
<td>0.15</td>
</tr>
<tr>
<td>ACEi/ARB, n (%)</td>
<td>32 (65)</td>
<td>26 (52)</td>
<td>0.22</td>
</tr>
<tr>
<td>Fruiseride, n (%)</td>
<td>45 (91)</td>
<td>49 (98)</td>
<td>0.20</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>10 (20)</td>
<td>17 (34)</td>
<td>0.17</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>13 (26)</td>
<td>13 (26)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Pharmacologic management – HFREF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers, n (%)</td>
<td>7 (53)</td>
<td>17 (71)</td>
<td>0.47</td>
</tr>
<tr>
<td>ACEi/ARB, n (%)</td>
<td>6 (46)</td>
<td>12 (50)</td>
<td>1.00</td>
</tr>
<tr>
<td>Fruiseride, n (%)</td>
<td>12 (92)</td>
<td>23 (95)</td>
<td>1.00</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>4 (30)</td>
<td>9 (37)</td>
<td>0.73</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>5 (38)</td>
<td>6 (25)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Appropriate prescription/non-prescription of medications in HFREF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers, n (%)</td>
<td>11 (84)</td>
<td>21 (87)</td>
<td>1.00</td>
</tr>
<tr>
<td>ACEi/ARB, n (%)</td>
<td>13 (76)</td>
<td>19 (79)</td>
<td>1.00</td>
</tr>
<tr>
<td>Spironolactone, n (%)</td>
<td>6 (46)</td>
<td>16 (67)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

\(^1\)Total number of patients who had beta-blockers, ACEi/ARB and spironolactone prescribed for correct indication (i.e. HFREF) and if not prescribed, contraindications for non-prescription (e.g. hyperkalaemia, orthostatic hypotension, etc.) were clearly documented. Total ‘n’ for appropriateness is larger than the ‘n’ for pharmacologic management as patients with appropriate non-prescription have been taken into account. ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; BP, blood pressure; HFREF, heart failure with reduced ejection fraction; UEC, urea and electrolytes.
ours support a model of care in which members of the multidisciplinary teams can be empowered to address and educate effectively specific patient goals in heart failure management. Further, such an approach may easily be extended to include other members of Allied Health. However, in order for this approach to be successful, sustained strong multidisciplinary leadership is required and a mature organisational culture of collaboration for patient safety and improvement in care delivery.

Our study demonstrated high compliance rates with daily weight and fluid balance monitoring by ward nurses, even before implementation of the care programme. This is likely due to well-established nursing practices, which are already ingrained into the routine care of patients with ADHF. Weight and fluid intake monitoring is an important aspect of heart failure management, a process which starts as inpatient and continues post-discharge.10–12 We found that opportunities exist where routine nursing practices can be translated into patient education. As patients’ acute clinical condition improves, ward nurses can start encouraging patients to monitor their own weight and fluid balance independently under supervision whilst still in hospital, thereby further reinforcing knowledge and confidence in self-management.7,12

Alongside medical doctors, ward nurses can therefore play a vital role educating the ‘action plan’ to the patient prior to discharge.

With regards to medications, in-hospital initiation of neurohormonal antagonists has been demonstrated to increase their continued long-term use after hospital discharge.3,13,14 Although our pharmacologic prescription rates were lower than published national data,15 due to our unique patient cohort of predominant elderly with multiple co-morbidities, they were comparable to prescription rates from other major centres serving similar type of patient population.16 Orthostatic blood pressure measurements may help guide medication titration in these patients, who are also at risk of falls.

Despite improvements in these process measures, we found that implementation of GM-HFCP did not improve readmission and mortality rates in our study. However, readmission rates in our study were similar to previously published data, which vary between 20 and 49% within 1–6 months of discharge.17,18

Our study has several limitations. First, the sample size was relatively small, which may limit the ability to demonstrate differences after the intervention. Second, the implementation period was relatively short. As with all quality improvement studies, delivery of well-resourced education programmes, repeated reinforcement of messages delivered over a longer period and promoting organisation culture in patient safety and care improvement are the key to success.19 Third, we conservatively assumed that lack of documentation on medical notes meant education was not provided whilst this may not have been the case. Fourth, only objective clinical outcomes were captured. Other patient-centred outcomes such as degree of understanding and satisfaction with the education content, attitude toward medication burden and confidence levels in managing heart failure on own were not measured, neither was staff satisfaction nor staff time involved. These outcomes could potentially influence the success rates of programme implementation. Finally, although this study was conducted in a well-resourced institution based on national guidelines, this may not necessarily reflect routine practice or resource availability at other institutions.

Despite these limitations, we showed that a multidisciplinary care programme in a busy general medical ward improved many aspects of heart failure care. We employed a before-and-after observational study design to avoid the Hawthorne effect by care providers, which may be associated with cross-over or step-wedge trial designs. Improvements to this model of care should be further explored in well-structured pragmatic randomised controlled trials, and practice incorporated into routine heart failure care or care bundles, which are currently being implemented at our institution.

**Conclusion**

This prospective observational study demonstrated that it is possible to share the roles of a heart failure nurse amongst members of the multidisciplinary team, with similar rates of delivery of pharmacologic and non-pharmacologic management aspects. This study also found that routine nursing practices can be translated into patient education. Future models can be further refined based on our model, which takes the ‘divide and conquer’ approach, sharing responsibility and accountability toward a common treatment goal together as a unit. Structured quality improvement research employing a cluster randomised control design can further identify strategies to encourage multidisciplinary teams to deliver innovative heart failure care.

**Acknowledgement**

We thank Mr Thomas Martin (Monash University) and Ms Kellie Easton (Alfred Hospital) for their invaluable help in the project.
References


Delays in presentation and diagnosis of pulmonary tuberculosis: a retrospective study of a tertiary health service in Western Melbourne, 2011–2014

Eloise Williams, Allen C. Cheng, Garry P. Lane and Stephen D. Guy

Abstract

Background: Effective tuberculosis (TB) control relies on early diagnosis and prompt treatment commencement.

Aim: To investigate delays in presentation and diagnosis of pulmonary TB (PTB) in a low incidence setting in Western Melbourne.

Methods: A single-centred retrospective observational cohort study of symptomatic patients ≥18 years newly diagnosed with PTB that were commenced on treatment between 1 December 2011 and 1 December 2014 at a tertiary teaching hospital in Western Melbourne. Main outcome measures included median duration of patient, health system and total delays to diagnosis of PTB and clinical factors associated with prolonged patient (>35 days) and health system (>21 days) delay.

Results: A total of 133 patients were included. The median (range) duration of patient, health system and total delay to diagnosis were 28 (0–610), 18 (0–357) and 89 (1–730) days respectively. Prolonged patient delay was associated with being from a country with an annual TB incidence of <50/100 000 (odds ratio (OR) 5.98, 95% confidence interval (CI) 1.19, 29.98) and diabetes mellitus (OR 3.02, 95% CI 1.04, 8.78) in multivariate analysis. Being Australian-born or a resident of Australia ≥6 years (OR 0.03, 95% CI 0.12, 0.74; OR 0.30, 95% CI 0.00, 0.033 respectively) was associated with reduced patient delay.

Conclusions: In this low-incidence, high-resource setting, patient delays contribute most to total delay in PTB diagnosis. Strategies addressing this aspect of the TB diagnosis pathway, such as health literacy and promotion programmes for new migrants and raised primary healthcare awareness, could have the largest impact on reducing total PTB diagnosis delays.

Introduction

Tuberculosis (TB) is a major global health problem; an estimated 10.4 million people developed TB in 2015 and 1.4 million people died from the disease. Early diagnosis and prompt commencement of treatment are important for effective TB control. Delayed diagnosis may worsen the severity of disease and increase the risk of death.

Australia has maintained an annual incidence rate of active TB of 5.2–7.0 cases per 100 000 since the mid-1980s. Of the 1263 notified cases (nationally) in 2013, 58% had pulmonary tuberculosis (PTB). Over the past decade, Australia has experienced a modest increase in TB incidence, from a rate of 5 per 100 000 in 2003 to 6.2 per 100 000 in 2011. This is likely due to an increasing migrant population from high-incidence regions of the world; 88% of patients diagnosed with TB in Australia in 2013 were born overseas. In comparison to the risk of active TB (over the past 10 years) in the Australian-born population of approximately 1 in 100 000, the risk of Australian immigrants reflects the TB incidence in the individual’s country of origin. The risk of active TB is highest for individuals in the first 6 years after migration, and approximates 100–150 per 100 000 person-years for those from Asia, Africa and the Pacific during this period. Risk then falls to approximately 50 per 100 000 person-years by 12 years.

Several studies in various international settings have investigated time delays in the diagnosis of PTB. Delays may occur before medical presentation (‘patient’ delays) or after medical presentation (‘health system’ delay).
Delays in diagnosis of tuberculosis

However, there is no consistent definition of ‘delayed’ (i.e. prolonged time until) diagnosis for PTB in the international literature. Previous studies have arbitrarily nominated a certain number of days from onset of symptoms to differentiate ‘delayed’ from ‘acceptable’ time periods; the number of days constituting ‘delayed diagnosis’, however, has varied widely. Definitions of total delay have varied from 28 to 98 days; patient delays have been defined variously from 30 to 60 days, and health system delays from 7 to 56 days.

Since the last study of delayed diagnosis in Australia 15 years ago, there have been major sociodemographic changes in the Australian population and new rapid tests for TB based on nucleic acid detection. We sought to explore factors associated with diagnostic delays in a large community hospital in Western Melbourne between 2011 and 2014.

Methods

Study design and setting

A retrospective cohort study of patients diagnosed and treated for PTB at a single health service in Victoria was undertaken between 1 December 2011 and 1 December 2014. Western Health is a multi-campus tertiary health service in the western suburbs of Melbourne (Victoria) that provides healthcare services to a population of approximately 800 000 people. Western Health treats approximately 25–30% of Victoria’s approximately 350 cases of TB each year.

Case finding, inclusion and exclusion criteria

Patients were identified by two methods: a hospital database of discharge coding and notification data from the Victorian Tuberculosis Program. In Victoria, the notification of confirmed cases of TB is required under state legislation. The medical records of all additional cases identified by Western Health Australian Discharge Related Group (A-DRG) codes for pulmonary or miliary TB (ICD-10-AM codes A15, A16 and A19) were reviewed.

Patients were included if they were symptomatic with PTB, including disseminated TB with lung involvement or extra-pulmonary TB at a contiguous site combined with PTB, and commenced on treatment between 1 December 2011 and 1 December 2014. Patients under 18 years, those with extra-pulmonary TB without pulmonary involvement and asymptomatic patients were excluded.

Definitions of delays and prolonged delays

Initial healthcare contact was defined as the date the patient reported attending a healthcare provider, whether in primary care or hospital-based secondary or tertiary health services. The date of ‘diagnosis’ was defined as the date of commencing anti-TB therapy consistent with previous studies. Patient delay was defined as the time of onset of symptoms suggestive of PTB until initial healthcare contact; health system delay as the time from first initial healthcare contact until diagnosis and hospital delay as time from hospital admission to diagnosis. Total delay was the sum of patient delay and health system delay. We defined a prolonged patient delay and prolonged health system delay as a duration greater than the median of the sample population, rounded up to the nearest 1 week.

Countries of origin were defined as high risk if the annual incidence of TB was ≥50/100 000 and low risk if the annual incidence of TB was <50/100 000 according to the WHO Global TB report, 2014. The nucleic acid test (NAT) used for rapid molecular diagnosis of TB in this population was the GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), a fully automated DNA-PCR technique for the detection of TB and rifampicin-resistance mutations.

Statistical analysis

Univariate and multivariate regression analyses were performed to determine factors associated with prolonged delays. Univariate analyses were performed first, and factors with P < 0.2 were considered for further analysis in the multivariate analysis. For final model selection, a modified backwards stepwise selection process was used, checking the effect of dropping variables on other odds ratios to obtain a parsimonious model. For all tests, two-sided P-values with an α ≤ 0.05 level of significance were used.

Ethical considerations

This study was approved by the Western Health Low Risk Human Research Ethics Panel prior to its commencement (project number LNR/15/WH/24).

Results

Patient inclusion

Of 331 patients identified, 133 patients met eligibility criteria and were included in the study (Fig. 1). Notably, 37 patients were excluded due to asymptomatic PTB, which may be more common at this health service due
to its role as the coordinating centre for visa screening of chest X-ray (CXR) abnormalities in Victoria.

**Patient demographics**

Of these 133 patients, median age was 35 years, and 67% were male (Table 1). Most spoke a language other than English at home (90%) and were born overseas (92%), most commonly from the Western Pacific Region, particularly from Vietnam (Fig. 2); 85% (85%) had migrated from a high-risk country, and 44% had resided in Australia <6 years. Only two (2%) were HIV positive.

**Radiology**

Of the patients, 130 had a CXR available, with median time from CXR to diagnosis of 13 days (IQR 4–36 days); 106 (80%) had CXR features suspicious of active PTB (Table 2). Of the patients, 82 (62%) had computed tomography (CT) of the chest performed, with a median time from CT until diagnosis of 9 days (IQR 2–29). All 82 patients who underwent CT chest had abnormalities found.

**Microbiology**

Of the patients, 110 had expectorated sputa sent for acid-fast bacilli (AFB) smear and mycobacterial culture; 39 (36%) patients had a positive AFB smear and 86 (78%) a positive sputum mycobacterial culture (Table 2). Median time from sputum assay to diagnosis was 4 days (IQR 2–29 days). Of the patients, 57 (43%) underwent bronchoscopy; median time from bronchoscopy until diagnosis was 4 days (IQR 1–13). Of the patients, 57 patients had NAT performed on sputum; 47 (83%) of these were positive. In those who had NAT performed on sputa, the yield of positive NAT in AFB smear-positive sputa was 33 of 35 (94%), whereas the

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Figure 1 Patient inclusion flow diagram.
Table 1: Patient demographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n = 133), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median [IQR] 35 [26–57]</td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Male</td>
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<tr>
<td>Native Language English</td>
<td>13 (10)</td>
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<tr>
<td>Employed</td>
<td>47 (35)</td>
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<td>Time since migration</td>
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<tr>
<td>Australian-born</td>
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<td>Less than 6 years</td>
<td>59 (44)</td>
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<td>6 or more years</td>
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<td>Low-risk country</td>
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<td>High-risk country</td>
<td>113 (85)</td>
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<td>Symptoms</td>
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<tr>
<td>Cough</td>
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<td>Productive cough</td>
<td>86 (65)</td>
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<td>Haemoptysis</td>
<td>25 (19)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>38 (29)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>38 (29)</td>
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<tr>
<td>Weight loss</td>
<td>75 (56)</td>
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<td>Sweats</td>
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<td>Fevers</td>
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<td>Fatigue</td>
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<td>Comorbidities</td>
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<td>Current smoking</td>
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<td>Excessive alcohol intake</td>
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<td>Diabetes mellitus</td>
<td>31 (23)</td>
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<td>Chronic liver disease</td>
<td>12 (9)</td>
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<tr>
<td>Asthma/COPD</td>
<td>18 (14)</td>
</tr>
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<td>Malignancy</td>
<td>7 (5)</td>
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<tr>
<td>HIV positive</td>
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<td>Injecting drug use</td>
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</table>

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IQR, interquartile range.

Table 2: Diagnostic and outcome data

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<th>Characteristic</th>
<th>Patients (n = 133), n (%)</th>
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<tr>
<td>Sputum</td>
<td>110/133</td>
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<tr>
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<td>39/110 (36)</td>
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<tr>
<td>Mycobacterial culture positive</td>
<td>86/110 (78)</td>
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<tr>
<td>NAT positive</td>
<td>47/57 (83)</td>
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<td>Bronchoscopy specimen</td>
<td>57/133 (43)</td>
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<tr>
<td>AFB smear positive</td>
<td>9/57 (16)</td>
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<tr>
<td>Mycobacterial culture positive</td>
<td>42/53 (79)</td>
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<tr>
<td>NAT positive</td>
<td>29/43 (67)</td>
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<td>Overall microbiology</td>
<td>122/133 (92)</td>
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<td>Positive</td>
<td>11/133 (8)</td>
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<td>Negative</td>
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<td>Radiology†</td>
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<td>130/133 (98)</td>
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<td>CXR suggests active PTB</td>
<td>106/130 (82)</td>
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<td>CXR – cavitation</td>
<td>29/130 (22)</td>
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<td>CT chest performed</td>
<td>82/133 (62)</td>
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<td>CT chest abnormal</td>
<td>82/82 (100)</td>
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<td>Diagnosis</td>
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<td>Pulmonary TB</td>
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<td>Disseminated TB</td>
<td>16 (12)</td>
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<td>Pulmonary TB with contiguous extra-pulmonary involvement</td>
<td>20 (15)</td>
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<td>Outcome</td>
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<td>Completed treatment</td>
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<td>Continued treatment</td>
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<td>Treated at another site</td>
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<td>Lost to follow up</td>
<td>3 (2)</td>
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<tr>
<td>Died</td>
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</table>

†Radiological features not mutually exclusive. AFB, acid fast bacilli; CXR, chest X-ray; NAT, nucleic acid test; PTB, pulmonary tuberculosis; TB, tuberculosis.

Figure 2: Patient country of birth, categorised by WHO Region. WHO Regions are SEARO: South-East Asia Regional Office; WPRO: Western Pacific Regional Office; EMRO: Eastern Mediterranean Regional Office; AFRO: Africa Regional Office; EURO: Europe Regional Office; PAHO: Americas Regional Office.
yield of positive NAT on smear-negative sputa was 14 of 27 (52%). Of the patients who had a bronchoscopy, 46 (81%) had NAT performed on the bronchoscopy specimen. The yield of positive NAT on smear-positive bronchoscopy specimens was 6 of 6 (100%), whereas the yield of positive NAT on smear-negative bronchoscopy specimens was 23 of 40 (58%). Of the 26 patients with a prospectively collected NAT, median time from NAT to diagnosis was 1 day (IQR 0–1 days).

### Delays

Patient delay was the predominant delay, with a median of 28 days from symptom onset until first health service contact (Table 3). Median health system delay was 18 days. We therefore defined a prolonged patient delay as more than 35 days and a prolonged health system delay as more than 21 days. According to this definition, 55 of 133 (41.3%) patients in this study had a prolonged patient delay, and 59 of 133 (44.4%) had a prolonged health system delay.

### Prolonged patient delay

In univariate analysis, prolonged patient delay was associated with weight loss (odds ratio (OR) 2.16, 95% confidence interval (CI) 1.06, 4.43) and inversely associated with presence of fatigue (OR 0.41, 95% CI 0.16, 0.99) (Table 4). In multivariate analysis, migration from a low-risk annual TB incidence country (OR 5.98, 95% CI 1.19, 29.98) was the strongest predictor of patient delay (Fig. 3). Weight loss (OR 2.23, 95% CI 1.00, 4.96) and diabetes mellitus (OR 3.02, 95% CI 1.04, 8.78) were also associated with prolonged patient delay. Conversely, migration to Australia ≥ 6 years prior or being Australian born was associated with reduced patient delay (OR 0.30, 95% CI 0.12, 0.74; OR 0.03, 95% CI 0.00, 0.33 respectively).

### Prolonged health system delay

In univariate analysis, patient age of 65 years or older (OR 3.07, 95% CI 1.21, 7.79) (Fig. 4) and patient review in the emergency department (OR 0.28, 95% CI 0.09, 0.72), review in the emergency department (OR 0.33, 95% CI 0.16, 0.69) or admission to hospital (OR 0.17, 95% CI 0.06, 0.46). Additionally, for patients who were able to expectorate sputum, AFB smear positivity (OR 0.23, 95% CI 0.09, 0.56) and NAT positivity (OR 0.14, 95% CI 0.03, 0.62) were associated with reduced risk of prolonged health system delay. Patients who had positive sputum NAT had a median health system delay of 9 days, compared with a median health system delay of 41 days in those who had a negative sputum NAT and 21 days in those who did not have a sputum sent for NAT. Having cavitation lesions on CXR (OR 0.25, 95% CI 0.09, 0.67) was also associated with reduced health system delay.

In multivariate analysis, patient age of 65 or older was associated with prolonged health system delay (OR 4.29, 95% CI 1.55, 11.89), whereas presence of cough (OR 0.09, 95% CI 0.01, 0.79) and being admitted to hospital were associated with reduced health system delays (OR 0.28, 95% CI 0.09, 0.92).

### Discussion

This single-centre retrospective review of delays in diagnosis of PTB in Western Melbourne illustrated that delays between symptom onset and treatment commencement are predominantly due to patient delay in presentation for care. The median duration of delays found in this study align with those found in an international systematic review of the topic in 2009, which included 52 studies and found an average patient delay of 28.7 days and average health system delay of 25 days. Findings are also comparable to the latest studies conducted in Australia on this topic.8,15

A study published in 2001 included 782 symptomatic, culture-positive cases of PTB based on Queensland Tuberculosis Control Centre TB case notification form data between 1985 and 1998. Median patient delay in this study was 29 days and median health system delay was 22 days. Despite advances in rapid diagnosis, delays are only marginally shorter than those described 15 years ago. A recently published study by Dale et al.13 involved 5106 Victorian patients identified through notification form data between 2002 and 2015 with PTB and extrapulmonary TB and compared the management of patients receiving private versus public healthcare. The median patient delay was 18 days and median healthcare delay was 22 days in those receiving public healthcare in this cohort. The duration of health care delay found by Dale et al. correlates well with our study. The discrepancy in patient delay between our study and that by Dale et al. may be a factor of information bias, with
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<th>Multivariate analysis</th>
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<td>P</td>
<td>OR (95% CI)</td>
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<td>≤65 years</td>
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<td>English spoken at home</td>
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<td>Time since migration</td>
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<td>&lt;6 years</td>
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<td>1.00</td>
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<td>49/121 (40)</td>
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the duration of symptoms prior to healthcare contact perhaps being less accurately recorded on a notification form compared to a more detailed file review, or it may be due to socioeconomic factors specific to the community served by this single-centre health service.

Of significant interest in our study population was the wide range of patient and health system delays that occurred. Whilst this will not impact the median delays for each locus of delay, when total delay is considered, a substantial increase in delay occurs. A quarter of patients had patient delays between 90 and 610 days and health system delays between 53 and 357 days. Whilst in our subsequent analysis, various delays have been analysed regarding their potential to reduce time to diagnosis, perhaps the biggest impact overall could be achieved by expediting diagnosis of the quartile of individuals who experience very long delays.

In this study, migration from a country with annual TB incidence of <50/100 000 population was the strongest predictor of patient delay, although only 7% of patients fell into this group. Whilst several putative explanations for this exist, it is possible that people from these ‘low-risk’ countries, especially those residing in Australia <6 years, may be less aware of TB as a disease state whilst still in the higher risk time period to develop active disease post-migration. Recent migrants from high-risk countries also had a longer delay than Australian-born patients, whereas Australian-born patients and those residing in Australia >6 years had reduced risk of delay. This may be due to greater health literacy and English language skills in longer-term residents and Australian-born individuals, facilitating access to healthcare. We speculate that poor access to healthcare, poor health literacy, fear that TB diagnosis could

Table 4

<table>
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<th>Variable</th>
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<th>Multivariate analysis</th>
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<tr>
<td>Hazardous alcohol intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11/18 (61)</td>
<td>2.53 (0.92, 7.03)</td>
</tr>
<tr>
<td>No</td>
<td>44/115 (38)</td>
<td></td>
</tr>
</tbody>
</table>

Bold values are statistically significant. CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NA, not appropriate; NI, not included in final model; OR, odds ratio; TB, tuberculosis.
Table 5  Risk factors for prolonged health system delay

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%) OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>16/24 (67) 3.07 (1.21, 7.79)</td>
<td>0.02 4.29 (1.55, 11.89)</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>43/109 (39)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20/44 (46) 1.07 (0.52, 2.21)</td>
<td>0.86</td>
</tr>
<tr>
<td>Male</td>
<td>39/89 (43)</td>
<td></td>
</tr>
<tr>
<td><strong>English spoken at home</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5/13 (39) 0.76 (0.24, 2.47)</td>
<td>0.65</td>
</tr>
<tr>
<td>No</td>
<td>54/120 (45)</td>
<td></td>
</tr>
<tr>
<td><strong>Australian born</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3/11 (8) 0.44 (0.11, 1.75)</td>
<td>0.23</td>
</tr>
<tr>
<td>No</td>
<td>56/122 (46)</td>
<td></td>
</tr>
<tr>
<td><strong>Employment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working</td>
<td>16/47 (34) 0.52 (0.25, 1.08)</td>
<td>0.08</td>
</tr>
<tr>
<td>Not working</td>
<td>43/86 (50)</td>
<td></td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51/124 (41) 0.09 (0.01, 0.72)</td>
<td>0.01 0.09 (0.01, 0.79)</td>
</tr>
<tr>
<td>No</td>
<td>8/9 (89)</td>
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<tr>
<td><strong>Haemoptysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7/25 (28) 0.42 (0.16, 1.08)</td>
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</tr>
<tr>
<td>No</td>
<td>52/108 (48)</td>
<td></td>
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<tr>
<td><strong>Dyspnoea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17/38 (45) 1.02 (0.48, 2.18)</td>
<td>0.96</td>
</tr>
<tr>
<td>No</td>
<td>42/95 (44)</td>
<td></td>
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<tr>
<td><strong>Chest pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12/38 (32) 0.47 (0.21, 1.04)</td>
<td>0.06</td>
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<tr>
<td>No</td>
<td>47/95 (50)</td>
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<tr>
<td><strong>Weight loss</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33/75 (44) 0.97 (0.49, 1.93)</td>
<td>0.92</td>
</tr>
<tr>
<td>No</td>
<td>26/58 (45)</td>
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<tr>
<td><strong>Sweats</strong></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22/50 (44) 0.98 (0.48, 1.98)</td>
<td>0.95</td>
</tr>
<tr>
<td>No</td>
<td>37/83 (62)</td>
<td></td>
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<tr>
<td><strong>Fever</strong></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30/75 (40) 0.67 (0.33, 1.33)</td>
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</tr>
<tr>
<td>No</td>
<td>29/58 (50)</td>
<td></td>
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<tr>
<td><strong>Fatigue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9/31 (29) 0.43 (0.18, 1.01)</td>
<td>0.05</td>
</tr>
<tr>
<td>No</td>
<td>50/102 (47)</td>
<td></td>
</tr>
<tr>
<td><strong>Local medical officer review</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>44/94 (47) 1.41 (0.66, 3.02)</td>
<td>0.38</td>
</tr>
<tr>
<td>No</td>
<td>15/39 (25)</td>
<td></td>
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<tr>
<td><strong>Emergency department review</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27/80 (34) 0.33 (0.16, 0.69)</td>
<td>&lt;0.01 0.43 (0.17, 1.07)</td>
</tr>
<tr>
<td>No</td>
<td>32/53 (60)</td>
<td></td>
</tr>
<tr>
<td><strong>Outpatients review</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39/54 (72) 7.67 (3.51, 16.77)</td>
<td>&lt;0.001 NI</td>
</tr>
<tr>
<td>No</td>
<td>20/79 (25)</td>
<td></td>
</tr>
<tr>
<td><strong>Hospital admission</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39/107 (36) 0.17 (0.06, 0.46)</td>
<td>&lt;0.001 0.28 (0.09, 0.92)</td>
</tr>
<tr>
<td>No</td>
<td>20/26 (77)</td>
<td></td>
</tr>
<tr>
<td><strong>Current smoking</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16/48 (33) 0.49 (0.23, 1.01)</td>
<td>0.05</td>
</tr>
<tr>
<td>No</td>
<td>43/85 (51)</td>
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</tr>
</tbody>
</table>
impact visa and residency status within Australia, fear of associated costs of healthcare (even though TB services are provided free to all patients within Victoria) or stigma and misunderstanding about TB diagnosis and treatment may disproportionately affect recent migrants, and that structural barriers to TB care may exist.

Prolonged health system delay was more common in older patients, a finding common to a number of similar studies, including the previous Australian study.9 Predictably, there was reduced risk of prolonged healthcare delay in those with classical symptoms of cough, cavitating features on CXR and sputum AFB smear positivity. A positive sputum NAT was also associated with a shorter health system delay in this study. While delays were much shorter in patients admitted to hospital for investigation, this is likely to be confounded by the severity of illness and reverse causation (where patients are admitted because of a higher likelihood of TB and/or positive tests). Recommendations regarding where patients should be assessed for TB workup is therefore not possible from this dataset.

NAT and other molecular diagnostics appear to offer some utility in reducing diagnostic delays and may be the first of several new diagnostic tools available over the coming years. Vital to any strategy to reduce health system delay will be clinician education and awareness, consideration of PTB as a disease process and appropriately resourced facilities for diagnosis and management of PTB.

The limitations of this study include its retrospective nature, making it vulnerable to recall bias, with data concerning primary outcomes based on hospital records of symptom onset and nature recorded by medical officers rather than directly from patients. It was also limited to a single centre, which raises the possibility that findings are specific for this site; however, it is reassuring that a similar duration of health system delay was found in the recently conducted study by Dale et al.13

### Conclusion

This study demonstrates that patient delay remains the biggest delay in diagnosis of PTB, consistent with published literature. For greatest overall impact on reducing delays until TB diagnosis, strategies should continue to target migrants, especially those from high-risk countries, at several time points within their first years of residence within Australia. These may include health literacy programmes that assist new migrants with navigating the Australian healthcare system and information regarding TB disease, treatment and costs. These messages need to be framed in a culturally and linguistically contextualised manner to reach the populations most at risk. Engagement of community leaders with this issue to help disseminate these messages would be highly valuable. A letter to new migrants in the appropriate language explaining the importance of TB, the symptoms of active disease and that diagnosis and treatment will not incur costs or affect visa status could be another useful tool to address prolonged patient delays. The Australian Government Department of Immigration and Border Protection has developed an

### Table 5

Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Excessive alcohol intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6/18 (33)</td>
<td>0.59 (0.21, 1.67)</td>
</tr>
<tr>
<td>No</td>
<td>53/115 (46)</td>
<td></td>
</tr>
<tr>
<td>CXR shows cavity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6/29 (21)</td>
<td>0.25 (0.09, 0.67)</td>
</tr>
<tr>
<td>No</td>
<td>53/104 (51)</td>
<td></td>
</tr>
<tr>
<td>Sputum AFB smear positive (n = 110)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8/39 (21)</td>
<td>0.23 (0.09, 0.56)</td>
</tr>
<tr>
<td>No</td>
<td>38/71 (54)</td>
<td></td>
</tr>
<tr>
<td>Sputum mycobacterial culture positive (n = 110)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33/86 (38)</td>
<td>0.53 (0.21, 1.31)</td>
</tr>
<tr>
<td>No</td>
<td>13/24 (54)</td>
<td></td>
</tr>
<tr>
<td>Sputum NAT positive (n = 58)</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>13/47 (28)</td>
<td>0.14 (0.03, 0.62)</td>
</tr>
<tr>
<td>No</td>
<td>8/11 (73)</td>
<td></td>
</tr>
</tbody>
</table>

Bold values are statistically significant. AFB, acid fast bacilli; CI, confidence interval; CXR, chest X-ray; NAT, nucleic acid test; NI, not included in final model; OR, odds ratio.
excellent information web page\textsuperscript{14} in a number of languages for international students that could be more widely disseminated to all new migrants to Australia. Given that only 19.5\% of patients in this cohort identified as students, disseminating this information more widely could have a powerful effect. Additionally, healthcare providers to this group of patients require knowledge on TB disease, presentation and diagnostics as likelihood differs significantly from Australian-born individuals.

Acknowledgements

We acknowledge the Victorian Tuberculosis Program for their assistance with case finding through the provision of tuberculosis notification data.

References

BRIEF COMMUNICATIONS

Metformin-induced encephalopathy: the role of thiamine

Caoimhe McGarvey,1 Catherine Franconi,1 David Prentice2 and Michael Bynevelt3

Departments of 1Neurology, 2General Medicine, and 3Neurological Intervention and Imaging Service of WA, Royal Perth Hospital, Perth, Western Australia, Australia

Key words
metformin, encephalopathy, thiamine deficiency, haemodialysis, end-stage renal failure.

Abstract
A case of metformin encephalopathy is presented in a patient on haemodialysis for end-stage diabetic renal failure. The patient presented with frequent falls and clinical signs of Parkinsonism, on a background of recent anorexia and significant weight loss. Magnetic resonance imaging showed bilateral, symmetrical abnormalities centred on the lentiform nuclei. Metformin was withheld and signs and symptoms quickly resolved. We hypothesise that metformin may cause thiamine deficiency in patients with end-stage renal failure resulting in a specific metabolic encephalopathy.

Metformin is a rare cause of metabolic encephalopathy. Most reported cases occur in patients with end-stage renal failure (ESRF). Haemodialysis patients can present with various neurological disorders, including uremic encephalopathy, disequilibrium syndrome, dialysis-related dementia, stroke and infections.1 Thiamine deficiency as a cause of metformin encephalopathy has not been previously reported. We describe a case of metformin-induced encephalopathy and discuss thiamine deficiency as a potential aetiological mechanism.

A 44-year-old woman was transferred to our hospital from another health facility for investigation of frequent falls. The patient had ESRF secondary to diabetic nephropathy and had commenced haemodialysis 3 months previously. The patient’s past medical history included type 2 diabetes mellitus with associated retinopathy, hirsutism, hypothyroidism, hypertension and obesity.

The patient had experienced frequent falls and gait instability for 4 weeks prior to presentation. The falls were not associated with dizziness, chest pain, change in vision or altered sensation. Her family reported reduced speech volume. The patient had recent poor appetite and had lost 27.2 kg in weight over the preceding 3 months, her body mass index on admission was 36.1 kg/m². She denied smoking and any alcohol consumption. The patient had been recently commenced on metformin 1 g once daily but had been taking 1 g twice daily for 7 weeks. Other medications on admission were rosuvastatin, amlodipine, aspirin, moxonidine, prazosin, telmisartan and thyroxine. The patient had no known drug allergies.

On examination, respiratory rate was 18 breaths/min, oxygen saturation was >94% on 3 L O₂ through nasal prongs, heart rate was 75 beats/min, blood pressure was 185/80 mmHg with no postural drop and the temperature was 37.7°C. The patient was alert and orientated with a Glasgow Coma Scale of 15/15. Cardiovascular, respiratory and abdominal examinations did not reveal any abnormal findings. On neurological examination, all cranial nerves were intact with normal eye movements and no facial asymmetry or droop. However, marked hypophonia, facial hypomimia and dysarthria were noted. There was moderate cogwheel rigidity at both wrists and power was 5/5 throughout all four limbs. Reflexes were diminished but present in the upper limbs but ankle and knee jerks were absent bilaterally. Pinprick sensation was intact throughout and proprioception was normal. She was initially unable to stand, later demonstrating retropulsion and a shuffling gait. It was concluded her falls were related to her clinical extrapyramidal signs.

Haematology and biochemistry screen on admission: haemoglobin: 108 g/dL, white blood cell count: 6.7 × 10³/μL, platelet count: 216 × 10⁹/L, C-reactive protein: 43 mg/L, creatinine kinase: 251 U/L, creatinine: 345 mmol/L, urea: 9.1 mmol/L, potassium: 3.7 mmol/L, sodium: 140 mmol/L and bicarbonate:
25 mmol/L. Lactate on admission was 2.1 mmol/L. Liver function tests were deranged: bilirubin: 38 μmol/L, ALT: 92 U/L, ALP: 127 U/L, gamma gt: 58 U/L, albumin: 42 g/dL and total protein: 75 g/dL. Glucose was 9.7 mmol/L and a HbA1c 4 weeks prior to admission was 9.7 mmol/mol. The patient tested negative for human immunodeficiency virus and hepatitis B and C. Autoantibody and vasculitic screen was negative. Serum thiamine level was taken after replacement on Day 11 of admission and was 269 nmol/L (66–200 nmol/L).

A non-contrast enhanced computed tomography (CT) scan of the brain (Fig. 1) on the day of admission demonstrated symmetric low attenuation and swelling of the lentiform nuclei with surrounding oedema involving the internal and external capsule regions, head of the caudate nuclei and white matter of the temporal stems. There was no evidence of haemorrhage or hydrocephalus. A magnetic resonance imaging (MRI) of the brain performed 4 days later (Fig. 2) confirmed the basal ganglia and adjacent capsular abnormalities which were T2 hyperintense, also seen to involve the sub-insular regions, hypothalamus, optic tracts and chiasm. There was also a diffusion restriction along the posterior putamina bilaterally and magnetic resonance spectroscopy (two-dimensional chemical shift imaging at the level of the basal ganglia, echo time: 135 ms) demonstrated a persistent inverted doublet at 1.3 ppm consistent with the presence of lactate.

Suspecting the patient’s encephalopathy was related to metformin, the drug was withheld on admission and haemodialysis was arranged the day after hospital admission to facilitate the elimination of administered metformin. A detailed dietary diary revealed borderline dietary thiamine as a result of significantly reduced appetite since commencing dialysis. The patient recovered over the next few days without neurological sequelae and continues to have haemodialysis three times per week.

Discussion

Metformin-induced encephalopathy is a rare condition typically described in patients with ESRF. Reported findings in metformin encephalopathy include Parkinsonism and vasogenic oedema with T2 hyperintensity in the basal ganglia. Symptoms and signs improve on withdrawal of metformin.

Metformin is considered the first-line agent for the treatment of type 2 diabetes mellitus and has been shown to have numerous benefits, including a significant reduction in cardiovascular morbidity and mortality and is associated with a lower body weight and incidence of clinically significant hypoglycaemia compared to other treatments, such as sulphonylureas and insulin. The avoidance of metformin in conditions, such as chronic renal failure, cardiovascular disease and chronic hepatic and pulmonary conditions, has been recommended as it may potentially increase the risk of tissue anoxia and cause lactic acidosis.

However, a Cochrane review published in 2010, found no evidence that metformin increases the risk of the development of lactic acidosis. A more recent Cochrane registered controlled trial, published last year studied metformin use in chronic kidney disease (CKD) and found metformin was well tolerated in diabetes mellitus and CKD (stage III–V). No correlation was found between serum lactate and metformin dose or CKD stage. The finding of this report may lead to increased use of metformin in CKD with the potential to increase the incidence of metformin-induced encephalopathy.

Metformin exists primarily as a cation at physiological pHs, diffusing poorly across membranes. Metformin is therefore reliant on several cell membrane transporters for absorption, distribution and elimination. Of note, metformin is a substrate and competitive inhibitor of the human intestinal thiamine transporter, THTR-2 (SLC19A3), the major absorptive transporter of thiamine in the intestine. THTR-2 is similarly competitively inhibited by fedratinib, a Janus kinase 2 inhibitor, trialled as a treatment in patients with myelofibrosis. Fedratinib was withdrawn in the final stages of clinical trials after several patients developed Wernicke’s encephalopathy. The putative cause of thiamine deficiency was from the inhibition of THTR-2-mediated thiamine uptake. So far, thiamine levels have not been extensively measured with metformin use, but have however been showed to be reduced in CKD and diabetes mellitus.

After a review of the literature, we hypothesise that thiamine deficiency is a possible mechanism in metformin-induced encephalopathy as THTR-2 plays a major role in mediating the first step in thiamine absorption from the small bowel lumen to the enterocyte. It is conceivable that metformin may inhibit intracerebral thiamine transport, THTR-2 is also found in the brain so it is possible that metformin can locally interfere with thiamine transport.

The classic triad of Wernicke encephalopathy includes encephalopathy, gait ataxia and oculomotor dysfunction. Other clinical findings include acute confusion, delirium, ataxia, ophthalmoplegia, memory disturbance, hypothermia with hypotension, delirium tremens and amnesia. Typical MRI findings with Wernicke encephalopathy include T2 and fluid-attenuated inversion recovery hyper-intensity in the mammillary bodies, periventricular thalamus and periaqueductal grey.
CT imaging may show symmetrical, low-density abnormalities in periventricular areas, the diencephalon and the midbrain. These symmetrical lesions are uncommon in other cerebral encephalopathies. Atypical clinical and radiological features generally tend to occur in non-alcoholic Wernicke encephalopathy and have been described in the setting of chemotherapy, hyperemesis gravidarum, malnutrition and renal failure.

Our patient’s imaging findings are typical of those seen in metformin and other metabolic encephalopathies particularly in the setting of metabolic acidosis. Imaging findings as seen in our patient have been described in confirmed thiamine deficiency in haemodialysis patients. Hung et al. reported thiamine deficiency causing chorea in two patients on haemodialysis. Particular note is made of one patient having lost several kilograms of body weight in the previous 6 months due to poor appetite, while the other was severely malnourished on examination and thiamine deficiency was confirmed in the serum. Both patients presented with dysarthria and unsteady gait initially before progressing to chorea. Imaging in these patients was similar to that seen in our patient with CT Brain showing low-density changes in the basal ganglia and with MRI (in one patient) demonstrating T2 signal hyperintensity in the basal ganglia.

Dialysis patients are at particular risk of thiamine deficiency due to poor intake and accelerated loss of water-soluble vitamins during dialysis. Our patient had borderline dietary thiamine intake as per detailed dietary diary on a background of anorexia over a 3-month period. A case of metformin encephalopathy with similar clinical and radiological features to our case described by Kang et al. in 2013 also reported anorexia for 1 month prior to presentation in a patient on haemodialysis.

Hung et al. went on to investigate further haemodialysis patients presenting with altered mental status over a 1-year period and found that 30% of patients had confirmed thiamine deficiency that responded to intravenous thiamine. Their presentations included confusion, chorea, acute visual loss, rapidly progressive dementia, myoclonus, convulsions and coma. Although all patients in the study had elevated plasma lactate levels, severe lactic acidosis was only observed in 2 out of 10 patients with proven thiamine deficiency, one of whom had concurrent liver cirrhosis but the other had been administered metformin for glycaemic control.

There is a genetic model of impaired intracerebral thiamine transport recognised in the paediatric population.
As reported by Ortigoza-Escobar et al. in 2014, thiamine transporter 2 deficiency due to a recessively inherited mutation in the SLC19A3 gene, presents with acute dystonia and features of Leigh encephalopathy.\(^1\) These clinical symptoms and signs improve significantly with early administration of intravenous thiamine. This diagnosis was suggested by a characteristic MRI pattern of T2 hyperintensities with striatal and medial thalamic involvement in association with lactic acid accumulation and high organic acid excretion in affected infants.\(^1\)

We conclude that clinicians should have a high index of suspicion for metformin-induced encephalopathy in patients with ESRF on haemodialysis presenting with neurological abnormalities. We recommend large-scale studies on the effects of metformin in ESRF to characterise the true risk of lactic acidosis in regard to metformin use in states of tissue anoxia. Further studies are also needed to determine the prevalence of thiamine deficiency in all patients receiving metformin.

References

9. Pardanani A, Harrison C, Cortes JE, Cervantes L, Vedolin L, Rieder CR. Two additional cases of metformin-induced encephalopathy presenting with neurological abnormalities. We conclude that clinicians should have a high index of suspicion for metformin-induced encephalopathy in patients with ESRF on haemodialysis presenting with neurological abnormalities. We recommend large-scale studies on the effects of metformin in ESRF to characterise the true risk of lactic acidosis in regard to metformin use in states of tissue anoxia. Further studies are also needed to determine the prevalence of thiamine deficiency in all patients receiving metformin.

References

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Assessment of potential opioid toxicity and response to naloxone by rapid response teams at an urban Melbourne hospital

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Key words
naloxone, opioids, opioid toxicity, rapid response system.

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Abstract
Opioid prescriptions have significantly increased in recent years and are used for a wide variety of indications. Electronic medical records of 45 patients who received naloxone by a rapid response team over an 18-month period were retrospectively reviewed. This study found inconsistencies in the management of possible opioid toxicity with variation in the total naloxone dose and number of doses administered. This highlights the importance of a standardised protocol for recognition and management of opioid overdose.

Although pharmaceutical opioids have been recommended in the treatment of acute pain and cancer pain, the use of opioids has expanded in the last decade to include the treatment of acute and chronic non-cancer pain despite the limited evidence of the long-term benefits of opioid use for any indication.1–3 In Australia, there was a 15-fold increase in the number of Pharmaceutical Benefit Scheme listed opioid dispensing episodes (500 568–7 495 648) between 1992 and 2012.1

One of the main concerns about increased opioid prescriptions, coupled with prolonged use in patients with chronic non-cancer pain, is the potential for opioid-related harm. Between 2002 and 2011, the number of accidental deaths due to pharmaceutical opioids and illicit drugs in Australia increased from 151 to 266, representing a 1.7-fold rise.1 People at higher risk of opioid overdose include those with opioid dependence, those who inject opioids, patients who take more than 100 mg morphine (or equivalent) daily or who use opioids with other sedating substances, the elderly and those with comorbid health conditions.1,4

Opioid overdose can be identified by a combination of signs, including decreased conscious state, respiratory depression and miosis.3,5 Naloxone, an antidote to opioid poisoning, completely reverses the effects of opioid overdose if administered in time.3

Although opioids are widely prescribed in the acute hospital, specific methods to evaluate opioid toxicity in this setting are lacking. The aim of our study was to describe the assessment of potential opioid toxicity and its management. As naloxone is usually stored in crash carts, its use is not easily audited. Consequently, we assessed naloxone use by rapid response teams as a surrogate for cases of suspected opioid toxicity.

The study population included patients in an urban hospital in Melbourne, Australia who received naloxone by the rapid response team during a Code Blue or Medical Emergency Team (MET) call between January 2012 and June 2013. Electronic medical records of these patients were retrospectively reviewed. Data analysis was carried out using STATA version 11.2 (StataCorp, College Station, TX, USA). Ethics approval was obtained from the institutional ethics committee.

In total, there were 49 codes where naloxone was used involving 45 patients over this 18-month period. Forty (81.6%) of these codes were MET calls, five (11.1%) were Code Blues and four (8.9%) were MET calls subsequently escalated to Code Blues. The characteristics of these patients are described in Table 1.

Reduced conscious state was the main reason or one of the reasons for the code in 44 episodes (89.8%). Other documented reasons included hypoxia, hypotension and reduced respiratory rate. The respiratory rate prior to naloxone administration was clearly documented in 34 episodes. Of these, only 4 (11.8%) episodes had patients with a consistently documented respiratory rate of less than 12, 18 patients (52.9%) had a consistently normal respiratory rate (12–20) and 9 patients (26.5%) had a consistently increased respiratory rate greater than 20. Pupil size was commented on in...
37 episodes and of these, 17 (45.9%) episodes made a note of pupils being constricted.

Opioids taken in the 24 h prior to the emergency code were also reviewed. Opioid consumption was not clearly documented in three episodes and in one episode, the patient had not received any opioids in the preceding 24 h. Of the remaining episodes, we were able to convert the opioids consumed to an oral morphine equivalent in 33 episodes. Of these, patients in 16 episodes (48.5%) had more than 100 mg of oral morphine equivalent.

Overall, patients in 24 of the episodes (49.0%) had also received another sedating substance, such as an antipsychotic, antidepressant or benzodiazepine.

There was a wide range of naloxone doses administered. Nine episodes were excluded, as the naloxone dose administered was unclear either because it was not charted in the medication chart or there was a discrepancy between the medication chart and the patient’s notes. Of the remaining 40 episodes, the total naloxone dose given during the code itself ranged from 40 to 2000 micrograms with a mean dose of 367 μg. The number of doses given during the code was clearly documented in 23 episodes and ranged from one to six doses. One dose of naloxone was given in 16 episodes (69.6%). Two, three and four doses were given in two episodes each and six doses of naloxone were given in one episode.

The route of naloxone administration was clearly documented in 34 episodes. In 30 episodes (88.2%), naloxone was given intravenously only. Naloxone was given through both intramuscular and intravenous routes in three episodes (8.8%) and subcutaneously in one episode (2.9%). Only one episode included a stat dose followed by an infusion of naloxone.

The effectiveness of naloxone was documented in 46 episodes. Table 2 shows a comparison between the perceived effectiveness of naloxone for example, if the rapid response team thought there was an improvement in the patient’s conscious state, and whether the team believed opioids were implicated as a cause for the patient’s deterioration.

Discussion

The assessment of potential opioid toxicity in hospital is challenging as there are no systems in place that accurately track opioid prescribing or administration errors.
Our study demonstrates a need for improved education and practice guidelines around the recognition and management of opioid overdose. The opioid overdose symptoms of reduced consciousness, miosis and respiratory depression may not always be present. Respiratory depression is the sine qua non of opioid intoxication with a respiratory rate of 12 breaths/min or less strongly suggestive of acute opioid overdose. Miosis alone is insufficient to infer the diagnosis of opioid overdose particularly as it may be present in chronic opioid use, and polysubstance use may produce normally reactive or mydriatic pupils. Interestingly, a consistently reduced respiratory rate was documented in only four patients in this study. However, naloxone was noted to be effective in 39 episodes and opioids were implicated in 34 episodes. This raises concern regarding the diagnostic assessment of opioid toxicity and the appropriateness of naloxone administered. The deterioration of these patients could potentially be attributed to other factors such as disease progression or sepsis. It is important to note that patients on opioids will become more alert post-naloxone but this does not necessarily imply opioid toxicity.

The inconsistencies in the management of possible opioid overdose found in this study with wide variations in the total naloxone dose and number of naloxone doses administered are likely because of the lack of consensus regarding the definition of opioid overdose and its management. This study highlights the importance of having a standardised medical protocol in place to identify the clinical criteria for naloxone administration, as well as the recommended route and administration dose.

Choosing the effective dose of naloxone to be administered can be challenging as it depends on multiple factors including the amount of opioids received, the patient’s weight, and degree of penetrance of the opioid analgesic into the central nervous system. Boyer et al. recommends an initial naloxone dose of 0.04 mg for adults. If there is no response, the dose should be slowly increased every 2 min to a maximum of 15 mg. Naloxone has a shorter half-life than that of many opioids and some patients may require repeated doses to achieve satisfactory clinical outcomes. If multiple doses of naloxone are required, a naloxone infusion should be considered. Opioid toxicity is an unlikely cause if respiratory depression continues.

Naloxone may precipitate a short period of acute withdrawal symptoms which include hypertension, tachycardia, tremor, convulsion, confusion, headache and vomiting. Consequently, patients who have received naloxone should be monitored closely for side effects and pain scores post administration of naloxone should be appropriately documented.

Although MET calls and Code Blues are significant events during a patient’s hospital admission, there was inadequate documentation during and after these events particularly with regards to the adverse effects of naloxone. The poor documentation of these events and potential opioid toxicity as a complication in discharge summaries were also concerning. It is vital that complications during the admission are communicated to the local doctor as it may reduce irrational or inappropriate opioid prescribing in the community. The relatively small data set and the lack of adequate documentation in some episodes were potential limitations; the latter was an important finding highlighting the need for education about the importance of adequate, accurate and structured documentation during rapid response systems as well as in discharge summaries.

In conclusion, true and significant opioid toxicity in acute hospitals is relatively infrequent; however, education and guidelines about diagnosis, management and documentation of opioid overdose need improvement. This study presents a useful approach to assessing the use of naloxone in the acute hospital setting during rapid response systems as a surrogate for suspected opioid toxicity, and will allow comparisons and change to be assessed over time.

References

Lipid-lowering therapy use and achievement of cholesterol targets in an Australian diabetes clinic

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Key words: diabetes, lipid-lowering therapy, endocrinology, cholesterol, cardiovascular disease.

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Abstract

We documented temporal changes in the use of lipid-lowering medications and achievement of cholesterol targets in an Australian diabetes clinic. The number of patients using lipid-lowering therapy for primary or secondary cardiovascular prevention increased from 6 to 69% between 1993–1995 and 2014–2016, which corresponded to a decrease in low-density lipoprotein cholesterol levels from 3.7 to 2.4 mmol/L (P < 0.01).

Patients with diabetes are at high risk for the development of cardiovascular (CV) disease. Statins have been shown to reduce CV events in direct relationship to their low-density lipoprotein cholesterol (LDL-C)-lowering effect. However, there have been no long-term studies documenting the achievement of LDL-C targets and the uptake of lipid-lowering medications in patients attending diabetes clinics in Australia. Our objective was to document temporal changes in LDL-C levels and the use of lipid-lowering medications in patients attending diabetes clinics at an Australian university teaching hospital.

We studied patients attending diabetes clinics at St Vincent’s Hospital Melbourne, Australia with ethical approval for this quality assurance project being obtained from St Vincent’s Research and Governance Department Melbourne. Information was extracted from a clinic database from 1993 to 2016. The patient population had a mean age of 62.8 years (62.8 ± 19.11), of which, 75.9% had type 2 diabetes and 18.2% had a history of CV disease (CVD). We determined the percentage of patients on lipid-lowering therapy and LDL-C levels and grouped the data by number of patients results in order to ensure that a minimum overall sample size was greater than 30 patients per 3-year observation period and then represented the results as a line of best fit using lowess smoothing. All analysis was done using STATA 14.1 (StataCorp, College Station, TX, USA).

Figure 1 shows that the use of anti-lipid therapy increased from 6 to 69% of patients between the time periods 1993–1995 and 2014–2016 (P < 0.01). This corresponded to a decrease in LDL-C levels from 3.7 to 2.4 mmol/L (P < 0.01). There was a strong negative correlation between anti-lipid therapy use and LDL-C levels (r = −0.88, P < 0.01). The publication dates of three major ‘statin-trials’, arbitrarily selected for illustrative purposes only, in subjects with and without diabetes are also shown on the diagram, that is, The Scandinavian Simvastatin Survival Study (4S), Primary prevention for CVD with atorvastatin in type 2 diabetes (CARDS) and the CV benefits and diabetes risks of statin therapy in primary prevention (JUPITER). In patients with and without a history of CVD, the use of anti-lipid therapy and LDL-C levels achieved at eight different observation periods during the study period is shown in Table 1. Patients with or without a history of CVD had a decrease in mean LDL-C from 1993–1995 to 2014–2016 of 3.55 to 2.29 (P < 0.01) and 3.67 to 2.52 mmol/L (P < 0.01), respectively. There was a similar decrease in non-high-density lipoprotein cholesterol levels in patients from 4.66 to 3.22 mmol/L (P < 0.01) between 1993–1995 and 2014–2016, respectively. In general, the percentage of patients who had achieved lipid-treatment targets that were current at the time the data were collected were found to have increased. For 1992–1995, 35.8% were meeting the 1992 American Diabetes Association (ADA)
LDL-C target of <3.36 mmol/L, in 2004–2006 this rose to 46.3%, reaching the target of <2.60 mmol/L set in 2003 by the ADA. In 2013, targets were introduced by the ADA with specific reference to CVD history with 66.5% of our patients without a history of CVD meeting a LDL-C target of 2.60 mmol/L during 2013–2015. However, only 29.4% with a history of CVD met the target of <1.80 mmol/L. Similar results have been reported for the community-based Australian, Fremantle Diabetes Study 1 and 2 which ran during 1993–1996 and 2009–2011 and saw a reduction in LDL-C from 3.3 to 2.3 mmol/L. These studies were also able to show a similar uptake of lipid-lowering therapy from 11 to 68%. In the years 2010–2016, the breakdown of lipid-lowering medication was 79% for statins, 14% for fibrates, 5% for ezetimibe and 2% for other agents. During the years 2010–2016, the majority of patients (44%) taking a statin were on a dosage greater than or equal to 40 mg/day, 23% were taking a dose between 20 and 40 mg/day and 33% took a dosage less than 20 mg/day. Information regarding the type of lipid-lowering therapy prescribed for patients attending our clinic was not available prior to 2010.

The results of our audit suggest that there has been a substantial increase in the use of lipid-lowering therapies by patients with diabetes over the last 20 years, which has resulted in a significant improvement in LDL-cholesterol levels. It should be noted that our clinic population includes patients with type 1 and type 2 diabetes. There are known limitations in the use of the Friedewald equation for the calculation of LDL-C in patients with elevated triglyceride levels. For this reason, patients with a triglyceride level >4.5 mmol/L were not included in our audit. Although statin therapy is recommended for the vast majority of patients with diabetes, the use of statins in very young patients with type 1 diabetes may not be warranted. The above trends appear to be influenced by the publication of the results from major statin trials. A preliminary analysis of the HbA1c and blood pressure data over time from our clinic found a lack of improvement compared to the significant reduction in LDL-C. In the STENO-2 study, patients with type 2 diabetes in the conventional arm only experienced minor reductions in HbA1c (0.2 ± 0.3%), systolic blood pressure (~3 ± 3 mmHg) and diastolic blood pressure (~8 ± 2 mmHg) over 8 years. The STENO-2 study showed a reduction of 0.72 ± 0.33 mmol/L in LDL-C in the conventional therapy arm.

The risks and benefits associated with statin use have been a recent topic for discussion both in the medical and broader community. A recent review has suggested that for every 10 000 patients treated with an effective statin regimen for 5 years, there are five cases of myopathy, 50–100 of new onset diabetes and 5–10 of

Table 1 LDL-C measurements and cardiovascular disease history

<table>
<thead>
<tr>
<th>Year</th>
<th>History of CV disease</th>
<th>No history of CV disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean LDL-C</td>
<td>n</td>
<td>Mean LDL-C</td>
</tr>
<tr>
<td>1993–1995</td>
<td>3.55 (1.7, 6.3)</td>
<td>37</td>
<td>3.67 (1.40, 8.90)</td>
</tr>
<tr>
<td>1996–1998</td>
<td>2.85 (2.46, 3.24)</td>
<td>64</td>
<td>3.18 (1.17, 4.44)</td>
</tr>
<tr>
<td>1999–2001</td>
<td>2.30 (2.36, 3.64)</td>
<td>212</td>
<td>3.19 (2.20, 4.12)</td>
</tr>
<tr>
<td>2002–2004</td>
<td>2.50 (1.17, 3.71)</td>
<td>378</td>
<td>2.38 (1.32, 4.23)</td>
</tr>
<tr>
<td>2005–2007</td>
<td>2.48 (0.97, 3.38)</td>
<td>301</td>
<td>2.64 (1.32, 3.82)</td>
</tr>
<tr>
<td>2008–2010</td>
<td>2.14 (0.98, 4.4)</td>
<td>478</td>
<td>2.43 (0.99, 4.13)</td>
</tr>
<tr>
<td>2011–2013</td>
<td>2.09 (0.27, 5.55)</td>
<td>427</td>
<td>2.27 (0.23, 5.54)</td>
</tr>
<tr>
<td>2014–2016</td>
<td>2.29 (0.03, 6.72)</td>
<td>831</td>
<td>2.52 (0.14, 6.09)</td>
</tr>
</tbody>
</table>

Only the first LDL-C level available for an individual patient per time period was included in this analysis. Patients were classified as having a history of CV disease if they had one of the following: acute myocardial infarction, stroke, coronary artery bypass graft, angioplasty or carotid artery disease. CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.
haemorrhagic strokes.\(^1\) It is estimated that for every year an individual takes a statin, the risk of a major vascular event or the need for coronary revascularisation decreases by 25% for each mmol/L reduction in LDL-C, with absolute benefits being dependent on an individual’s background CV risk profile.\(^1\) Although these rates may be lower than seen in clinical practice, our clinic does not routinely systematically collect information on statin myopathy incidence.

There is a range of varied recommendations for the commencement for lipid-lowering therapy and targets for LDL-C levels. These range from assessments based on an individual’s risk factors to group-based risk-level assessment as advocated by The Canadian Cardiovascular Society.\(^1\) These Canadian Cardiovascular Society recommendations advocate the use of statins in any patients with diabetes over the age of 40, diabetes patients with microvascular disease or type 1 patients over the age of 30 who have had diabetes for more than 15 years.\(^1\) These guidelines also recommend targeting a LDL-C level of below 2.0 mmol/L in the primary prevention setting. The US Preventative Services Task Force released an updated version of their 2008 recommendations regarding statin use in November 2016. They recommend the use of low-to-moderate dose statins in adults aged 40–75 years without a history of CVD but with one or more risk factors, including diabetes, and a 10% or greater risk of experiencing a CV event during the next 10 years. The guidelines suggest using the Pooled Cohort Equations to calculate 10-year risk of CVD as developed by the American College of Cardiology and American Heart Association.\(^1\) The Australian College of General Practitioners bases their recommendation for the use of statins in patients with type 2 diabetes on an assessment of each individual’s absolute CV risk and also recommend a LDL-C target of <2 mmol/L.\(^1\) The National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand recommend a general primary prevention target of <2.0 mmol/L and a secondary prevention target of <1.8 mmol/L.\(^1\)\(^6\) Our results suggest that there has been a substantial decrease in LDL-C in patients with diabetes who do not have a clinical history of CVD. This most likely reflects the appreciation of the increase CVD risk that a diagnosis of diabetes conveys and the proven benefits of statins for the primary prevention of CVD in diabetes.\(^1\)

The release of generic statins, and regulatory interventions aimed at reducing the cost of many medications, should improve access to statin therapy for many patients with diabetes, who currently do not fulfil the Pharmaceutical Benefit Scheme indications for subsidised prescriptions. The impact of these changes on the actual uptake of statins and expected corresponding drop in LDL-C levels await to be documented by future audits. The use of newer lipid-lowering therapies, such as the PCSK9 inhibitors, although not currently routinely used in patients with diabetes shows promise, with some early studies showing a greater mean reduction in LDL-C when treated with a PCSK9 inhibitor compared to standard treatment with statins in patients with type 2 diabetes.\(^7\)

**References**


14 Anderson TJ, Gregoire J, Pearson GJ, Barry AR, Couture P, Dawes M et al. 2016 Canadian cardiovascular society...
Management of neurosyphilis: time for a new approach?

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Key words
syphilis, neurosyphilis, syphilis serology, rapid plasma reagin, cerebrospinal fluid.

Abstract
Given the long term sequelae of untreated neurosyphilis and insensitive tests to detect treponemes in the cerebrospinal fluid, questions regarding the utility of a lumbar puncture and cerebrospinal fluid analysis either to confirm or exclude neurosyphilis are raised.

Syphilis has been afflicting humans for over 500 years and no manifestation of the infection has been as troublesome as that of neurosyphilis. Existing definitions of neurosyphilis require evidence of Treponema pallidum invasion of the central nervous system (CNS) and yet there is no single available cerebrospinal fluid (CSF) test that is both sensitive and specific enough for this purpose.1 We are currently in the midst of a local Australian syphilis epidemic with notification rates increasing from 5.1 cases per 100 000 men per year in 2005 to 15.9 cases per 100 000 men in 2014, particularly in the population of men who have sex with men.2 Similarly, notifications are increasing across Europe and the United States.3,4

Whilst syphilis is notifiable, in most countries, a diagnosis of neurosyphilis is not, so there has been no published data documenting a rise in neurosyphilis diagnoses per se; however, anecdotally this appears to be the case. Clinicians everywhere are more and more likely to see patients presenting with a possible diagnosis of neurosyphilis. Now is a useful time to re-examine the limitations and pitfalls of available diagnostics and possibly consider a new approach of treating such patients with consistent eye, ear or other neurological symptoms with 15 days of intravenous penicillin without the requirement for CSF examination.

The neurotropic nature of T. pallidum has been appreciated for well over a century with early attempts to abort dissemination and CNS disease, even by excision of primary chancre, proving futile! Experimentally, T. pallidum is detectable within the bloodstream within

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48 h and in the CSF within 2 weeks following cutaneous inoculation.5,6 During the early 20th century, large cohorts of patients underwent lumbar puncture and CSF analysis in an attempt to address the question regarding the prevalence of neuroinvasion of T. pallidum. It was found that 15–30% of all stages of syphilis were associated with CSF abnormalities (predominantly elevations in protein and white cell counts) – the overwhelming majority without localising symptoms to the CNS.5,8 These findings have been replicated in contemporary studies in the human immunodeficiency virus (HIV) era leading to the concept of ‘asymptomatic neurosyphilis’, a syndrome believed to be the precursor of symptomatic neurosyphilis.9,10 However, the variables promoting progression from asymptomatic neurosyphilis to symptomatic neurosyphilis are unknown, although advanced immunosuppression with low CD4 count in the HIV population has long been thought to be a risk factor.11–13 The value of screening HIV patients with low CD4 count and positive serum syphilis serology for evidence of asymptomatic neurosyphilis and subsequent treatment of patients with a ‘CSF paretic formula’ (characterised by elevated protein and white cell count but, negative serology) as for neurosyphilis is still a cause for ongoing debate.14,15 An open-label, prospective randomised clinical trial at the University of Washington (Clinical Trials Registry number NCT02031146) hopes to answer this question by demonstrating that a strategy of immediate lumbar puncture followed by therapy based on CSF findings results in better serological and functional outcomes in patients at 6 and 12 months.

While several diagnostic algorithms exist for neurosyphilis possibly the most widely accepted is described by Sena et al. in the Manual of Clinical Microbiology.16 This algorithm mandates that a patient must have a positive serum treponemal test and a clinical syndrome compatible with neurosyphilis with one of three CSF tests positive; a reactive CSF Venereal Disease Research Laboratory (VDRL) test, a positive T. pallidum polymerase chain reaction (PCR) or identification of treponemes in nervous tissue by histological methods.16 Therefore, based on these criteria, a diagnosis of neurosyphilis is possible at any clinical stage of syphilis infection. This is in keeping with the scientific literature, including local experience at our institution, where CNS invasion with treponemes has been demonstrated at all clinical stages (i.e. primary, secondary, tertiary) of infection.1,7–9 Unfortunately, despite being the best available, there are still significant limitations with Sena et al.’s definition. We have not widely used the CSF VDRL in Australia for more than 20 years and the rapid plasma reagin that has largely replaced the VDRL is not validated for use in CSF nor is it as sensitive as the VDRL (67 vs 58%).16 Whilst hope was held that a T. pallidum PCR would have sufficient sensitivity to increase the diagnostic accuracy of CSF analysis, this has not proven to be the case. A study published in 2016 analysed 40 CSF samples from patients with documented neurosyphilis using a nested PCR targeting the tpp47 gene. Disappointingly the PCR gave a sensitivity of only 42.5% with a specificity of 97% when compared with a diagnosis based on clinical assessment and existing CSF diagnostic tests.17 T. pallidum PCR has found its place in the diagnosis of primary syphilis with superficial swabs of lesions of primary syphilis containing sufficient concentrations of treponemes for detection. Finally, examination of nervous tissue to demonstrate invasion of treponemes is neither justifiable nor practical in the majority of cases and is likely to be limited in the future to animal and autopsy studies.

The search for more sensitive and specific markers of CNS invasion of T. pallidum continues. Recent approaches include the use of quantitative CSF : serum ratios of treponemal antibodies (i.e. FTA-ABS) with higher ratios presumed to be indicative of intrathecal antibody production.18 These approaches attempt to improve sensitivity also by estimating permeability of the blood brain barrier with an albumin quotient. While these techniques, and others, appear to improve the sensitivity of existing CSF serology they are considerably more labour intensive than existing techniques and are yet to be validated or widely applied. CSF cytokine and chemokine profiling of patients with neurosyphilis has led to an expanding library of novel markers that correlate with CNS inflammatory responses and invasion of the CNS.18–20 A prospective study looking at the utility of CSF levels of chemokine CXCL 13 and T. pallidum DNA PCR to improve diagnostic accuracy in patients with suspected neurosyphilis has recently begun recruiting in Shanghai (Clinical Trials Registry number ChiCTR-DDD-16009591). Validation of these indicators will be difficult and further work is required before these tests can be confidently incorporated into any existing neurosyphilis diagnostic algorithm.

So, neurosyphilis continues to present both troublesome clinical syndromes for patients and a diagnostic dilemma for physicians. We are limited by a lack of understanding of disease pathogenesis, the unavailability of CSF tests with both an adequate sensitivity and specificity to confirm or exclude the diagnosis and considerable barriers to further clinical research. Furthermore, it is a heterogeneous syndrome, that may occur at any stage of the otherwise traditional temporal sequence of syphilis infection (i.e. primary, secondary, latent and tertiary), with manifestations that can include meningitis, meningovasculitis with stroke, uveitis and visual disturbance and otosyphilis that may present with vertigo, tinnitus or hearing loss. Late complications of untreated
neurosyphilis include cognitive impairment, dementia, psychosis, general paresis and tabes dorsalis. Add to this the insensitive and non-specific CSF tests available, and it is no wonder that clinicians struggle to confidently or exclude a diagnosis of neurosyphilis. Furthermore, later stages of syphilis are associated with low titre non-treponemal tests and an even lower chance of CSF abnormalities. Therefore, CSF examination in these patients is likely to be even less useful. Armed with an understanding of the limitations of CSF serology is now the time to have the discussion and collectively consider an alternative approach to patients who present with a clinically compatible syndrome with positive serum syphilis serology? We know of instances at our institution where patients with a high pre-test probability of neurosyphilis but negative CSF serology have been treated presumptively with 15 days of intravenous benzylpenicillin. Given the late consequences of untreated neurosyphilis and the current limitations with CSF analysis and tests, perhaps patients, at any stages of syphilis infection, with symptoms consistent with neurosyphilis and positive serum serology should be offered treatment with 15 days of benzylpenicillin? This then raises the question regarding the value of lumbar puncture and CSF analysis as part of a diagnostic evaluation in this cohort. In light of our current local syphilis epidemic perhaps now is the time to review collectively and reconsider our approach to this troublesome clinical syndrome.

References


8 Filides P, Parnell RJG, Maitland HB. The occurrence of unsuspected involvement of the central nervous system in unselected cases of syphilis. Brain 1918; 41: 255–301.


High urinary interleukin-8 levels is associated with poor prognosis in idiopathic membranous nephropathy
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Abstract
Biomarkers required to assess accurately the prognosis of idiopathic membranous nephropathy (IMN) are still unavailable. A retrospective study on 156 IMN patients showed only urinary IL-8 was associated with the achievement of initial complete remission (CR) in IMN patients. A urinary IL-8 level of less than 61.25 pg/mL was more sensitive for prediction of CR in IMN patients. Therefore, urinary IL-8 may be a potential biomarker for evaluating short-term prognosis of IMN patients.

Idiopathic membranous nephropathy (IMN) is a common immune-mediated glomerular disease and remains the leading cause of nephrotic syndrome in adults.1 The aetiology and optimal biomarkers required for evaluation of IMN prognosis remain unclear. Patients who achieved long-term complete remission (CR) have a lower risk for receiving renal replacement treatment.2 Many studies have failed to provide early, sensitive and specific biological markers for assessing the prognosis of IMN.3

More recently, it has been demonstrated that cytokines play a critical role as mediators of inflammation and as progressive factors in idiopathic nephrotic syndrome (INS).4 We recently examined serum levels of representative pro-inflammatory cytokines, including IL-8, IL-6, and IL-17 as well as the anti-inflammatory cytokine IL-10 was also examined as it is implicated in steroid resistance. Our studies indicated that only serum IL-8 levels were significantly increased in patients with steroid-resistance when compared to steroid-sensitive INS. Further studies indicated that intermittent high-volume haemofiltration (HVHF) promoted remission in steroid-resistant INS patients with volume overload and accompanied with IL-8 serum levels decreased,9 therapeutic efficacy of HVHF may partly be due to serum IL-8 clearance. However, whether IL-8 levels can be used to evaluate the prognosis of IMN remains unknown.

A total of 156 eligible patients with biopsy-proven IMN was included in this retrospective cohort study from January 2009 to December 2011, while another 46 healthy volunteers served as controls. The inclusion criteria included patients aged 18–75 years with biopsy-proven IMN and nephrotic syndrome, estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m², administration of glucocorticoids, angiotensin converting-enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). The exclusion criteria included secondary membranous nephropathy, infections, inflammatory diseases, cancers, acute kidney injury, acute liver injury and severe heart failure.

Initial therapy included the administration of glucocorticoids, which were administered to all patients followed by methylprednisolone pulse therapy with 500 mg/day for 3 days and oral prednisone 40 mg once daily in patients younger than 60 years of age. Alternatively, they were given methylprednisolone pulse therapy (250 mg/day) for 3 days, followed by oral prednisone administration (30 mg once) for those aged ≥60 years. After 8 weeks of prednisone treatment, patients were given cyclophosphamide (CTX) (0.6 g × 2, pulse therapy per 15 days, cumulative dose to 150 mg/kg), Tacrolimus (FK506) (0.05 mg/kg daily), or mycophenolate mofetil (1500 mg/day) for 6–18 months. The primary outcome measures were CR (defined as urinary protein excretion <0.3 g/day with serum albumin

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>3.5 g/dL and normal serum creatinine) and partial remission (PR) (defined as urinary protein excretion of 0.3–3.5 g/day and stable serum creatinine). Patients who achieved CR were examined every 3 months, while all others were evaluated on a monthly basis.

We enrolled 156 patients with IMN, of which 110 were male patients (70.5%). The median age was 54 (interquartile range: 43–61) years of age. Patients were divided into three groups according to immunosuppressive therapy type. The groups did not significantly differ in sex, systolic and diastolic blood pressure, serum creatinine, eGFR, serum uric acid, fibrinogen or time from diagnosis to biopsy. The median observation period for the entire cohort was 23 months. A total of 57 patients (36.5%) achieved CR, 82 patients (52.6%) achieved PR, 17 patients (10.9%) were classified as no response. The mean time to CR was 6.0 months. The cumulative probability of CR was not significantly different between treatment groups (log Rank $X^2 = 3.696, P = 0.158$). And the cumulative probability of PR was not significantly different between treatment groups (log Rank $X^2 = 0.256, P = 0.88$). Urinary IL-8 and IL-17 levels in all three groups of patients were significantly higher than in healthy control subjects ($P < 0.01$). Univariate Cox proportional hazards models and multivariate Cox proportional hazards model analysis indicated only urinary IL-8 levels were associated with initial CR (HR, 0.957; 95% CI, 0.937–0.977; $P = 0.000$) in patients with IMN.

The receiver operating characteristic curve analysis indicated the area under the receiver operating characteristic curve (AUROC) in urinary IL-8 levels generated an optimal cut-off of 61.65 pg/mL (Youden point). The AUC was 0.677 (95% CI 0.586–0.768; $P = 0.000$), with the sensitivity and specificity 0.83 and 0.51 respectively (Fig. 1A). Patients with IMN were divided into two groups: urinary IL-8 levels $>61.65$ pg/mL ($n = 110$), defined as the high-IL-8 group, and urinary IL-8 levels $<61.65$ pg/mL ($n = 46$), defined as the low-IL-8 group. The cumulative probability of CR in the low-IL-8 group patients was significantly higher than that of the high-IL-8 group patients (log Rank $X^2 = 17.79, P = 0.000$)(Fig. 1B). With 61.65 pg/mL used as a threshold, 63% of patients with urinary IL-8 levels less than 61.65 pg/mL achieved CR. This contrasted to only 25.5% of patients with urinary IL-8 levels greater than 61.65 pg/mL achieving CR ($P < 0.001$).

**Discussion**

This study is the first to evaluate the association of cytokines and their effect on short-term outcomes of patients with IMN. Previous studies identified several clinical predictors of poor renal outcome in IMN patients including male sex, age > 50 years, hypertension, severity of proteinuria, elevated serum creatinine level at the time of diagnosis and chronic renal tubular interstitial changes.10–12 Our study indicated that age, male sex, systolic and diastolic blood pressure, serum creatinine, urinary protein excretion, serum albumin, eGFR, serum uric acid, serum cholesterol, serum triglyceride, haemoglobin, fibrinogen and ACEI (or ARB therapy) were not
associated with initial CR. Therefore, the routine clinical, laboratory and pathology indicators do not evaluate sufficiently the short-term outcomes of patients with IMN.

Some studies suggesting that IMN is primarily an immune disease resulting from immunoregulatory imbalance between T helper subtype 1 (Th1) and T helper subtype 2 (Th2).13,14 The mechanisms through which T-cells affect the course of IMN remain unclear. However, there may be circulating factors released from activated T-cells which affect the pathogenesis of IMN.

Our study showed that only urinary IL-8 was associated with the achievement of initial CR. The patients with CR had significantly lower IL-8 levels than those patients who had not achieved initial CR. IL-8 is a proinflammatory cytokine produced by endothelial cells and macrophages that attracts neutrophils and lymphocytes to the site of inflammation.5 Early studies revealed that the IL-8 gene is predominantly expressed in peripheral blood mononuclear cells and that serum IL-8 concentration is increased in patients with INS.15 Several studies have reported elevated serum IL-8 levels in the nephrotic phase when compared with the remission phase. Urinary IL-8 was significantly higher in relapsed SR than in SS patients in remission. This increased urinary IL-8 levels was associated with local changes in glomerular permeability.16,17 Therefore, IL-8 may be involved in the pathogenesis of IMN, higher urinary IL-8 levels may be associated with severe inflammation reaction in renal tissues and predict a bad clinical outcomes.

The study showed that urinary IL-8 concentration of 61.65 pg/mL was chosen as the optimal cut-off value for CR in patients with IMN. The AUROC was 0.677 with the sensitivity and specificity 0.83 and 0.51 respectively. The cumulative probability of CR in the low-IL-8 group (IL-8 levels >61.65 pg/mL) was significantly higher than that in the high-IL-8 group patients (IL-8 levels <61.65 pg/mL), therefore, a urinary IL-8 concentration greater than 61.65 pg/mL was considered higher risk to develop poor prognosis in IMN.

This study is unique in that it identifies new predictors for clinical outcomes among IMN patients. In conclusion, the study indicated that urinary IL-8 may be a significant short-term prognostic biomarker for IMN. Patients with lower urinary IL-8 levels were more likely to achieve CR.

References


Position Paper

Considerations for pre-transfusion immunohaematology testing in patients receiving the anti-CD38 monoclonal antibody daratumumab for the treatment of multiple myeloma

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Key words
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Abstract
In recent years, the anti-CD38 monoclonal antibody daratumumab (Darzalex; Janssen-Cilag Pty Ltd) has been shown to be highly efficacious in relapsed and refractory multiple myeloma, with the final results of treatment in newly diagnosed patients awaited. Despite awareness of the potential interference of daratumumab in pre-transfusion immunohaematology testing during phase I and II clinical studies, there was a degree of unpreparedness in the community upon the introduction of this drug into the clinics, particularly the impact that it has on the operational processes in hospital transfusion laboratories and timely issue of red blood cells (RBCs). Anti-CD38 interference in pre-transfusion immunohaematology tests is a particular problem in patients being treated with daratumumab for multiple myeloma as many will require RBC transfusions during their disease treatment. Panagglutination caused by anti-CD38 monoclonal antibody during the indirect antiglobulin test may mask the presence of a clinically significant RBC alloantibody in the patient’s plasma during the antibody screen and identification process, which may be overlooked, particularly in urgent situations, subsequently resulting in a delayed or acute haemolytic transfusion reaction. Here, we summarise daratumumab’s effects on pre-transfusion immunohaematology testing and its impact on clinical practice and make practical recommendations based on a consensus from medical and scientific transfusion experts and myeloma specialists on behalf of the Australian and New Zealand Society of Blood Transfusion and Myeloma Scientific Advisory Group to Myeloma Australia, respectively.

Introduction
In recent years, the anti-CD38 monoclonal antibody (mAb) daratumumab (Darzalex; Janssen-Cilag Pty Ltd) has been shown to be highly efficacious in relapsed and refractory multiple myeloma (MM). In 2015, daratumumab was granted accelerated approval by the Food and Drug Administration in the United States for the treatment of relapsed/refractory MM, with Australia’s Therapeutic Goods Administration (TGA) following suit in 2017. These decisions were based on results only from early phase I/II clinical studies, in which heavily pretreated patients with MM were shown to have an overall
survival improvement of approximately 11 months from single-agent daratumumab.1 As a result of this early move into the clinics, there was an underappreciation of the impact of daratumumab’s interference with pre-transfusion immunohaematology testing and, therefore, on hospital/pathology transfusion laboratory operational processes, timely issuing of blood, potential blood transfusion reactions and, ultimately, patient safety.

CD38 is an integral transmembrane glycoprotein that is expressed on many cell types and highly expressed on plasma cells. It has diverse functions, including enzyme activity, intracellular calcium regulation and receptor-mediated adhesion.2 It is also variably expressed on the surface of red blood cells (RBCs). Anti-myeloma activity from daratumumab occurs through anti-CD38-mediated immune mechanisms, including complement-dependent cellular cytotoxicity (CDCC), antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and immunoregulatory depletion of immune suppressive regulatory T cells.3–5 In addition, direct tumouricidal activity occurs through pro-apoptotic signalling pathways upon cross-linking of surface CD38. As an off-target side-effect, when bound to CD38 on RBC, daratumumab interferes with the indirect antiglobulin tests (IAT), a technique routinely used in pre-transfusion testing. Anti-CD38 interference in immunohaematology tests is a particular problem in patients being treated for MM as many will require blood transfusions as part of their supportive care during ongoing disease treatment. Panagglutination caused by anti-CD38 may mask the presence of a clinically significant RBC antibody (Ab) in the patient’s plasma, which may be overlooked, particularly in urgent situations, and subsequently result in an acute or delayed haemolytic transfusion reaction.

Here, we summarise daratumumab’s impact on pre-transfusion immunohaematology testing, its impact on clinical practice and provide practical recommendations based on a consensus from medical and scientific transfusion experts and myeloma specialists on behalf of the Australian and New Zealand Society of Blood Transfusion (ANZSBT) and Myeloma Scientific Advisory Group to Myeloma Australia (MSAG), respectively.

The nature of daratumumab’s interference with pre-transfusion tests

The binding of daratumumab to CD38 on human RBC is detected using the IAT (or indirect Coomb’s test) carried out at 37°C, which is the primary antibody screening method used to detect the presence of clinically significant alloantibodies. Secondary testing methods that may be used in antibody investigations, such as room temperature testing or immediate spin tests to check for ABO compatibility, do not detect the effects of daratumumab. There is some variability of expression of CD38 on RBC, and the presence of daratumumab in the patient’s plasma typically causes weak panagglutination in IAT used for pre-transfusion immunohaematology testing. In contrast, daratumumab does not interfere with ABO or RhD typing.6,7

In the antibody screen and antibody identification panel, the plasma of patients treated with daratumumab exhibits weak (1+ or 2+, using 0–4 scoring) panagglutination. This panagglutination occurs in all IAT tests, for example, saline, low ionic-strength saline (LISS) and polyethylene glycol (PEG), and all IAT methods, including column agglutination technology (CAT) and tube and solid phase.6 Positive IAT may persist for up to 6 months after discontinuation of daratumumab therapy.7–9 The presence of panagglutination must be investigated at each testing episode as the reactivity may mask the presence of a clinically significant alloantibody or the presence of autoimmune haemolytic anaemia.

Interestingly, while daratumumab in the patient’s plasma will cause agglutination in IAT with all reagent RBC and donor RBCs, reactivity with the patient’s own RBC is not consistent, and the auto-control in the antibody identification panel is frequently negative, as is the direct antiglobulin test (DAT). This suggests that the patient’s RBCs with high levels of CD38 may be cleared from the circulation and/or be subject to anti-CD38-mediated antigen downregulation,10 which may explain why, to date, clinical manifestations of daratumumab-related, immune-mediated haemolysis have not been reported in daratumumab-treated patients. That observation notwithstanding, interference by daratumumab has a serious impact on the ability of transfusion laboratories to perform timely pre-transfusion testing.11 The resolution of the interference requires time-consuming specialist investigations that inevitably lead to delays in the provision of blood for transfusion, especially if it is not known that the patient is being or has been treated with daratumumab. In addition, clinically significant RBC alloantibodies may be masked and overlooked, potentially resulting in an acute or delayed haemolytic transfusion reaction. For urgent or emergency transfusions, however, it should be possible to determine the patient’s ABO and RhD blood group and provide ABO-compatible blood, but provision of this without further investigation is not without risks.12,11

Overcoming the interference of anti-CD38 therapy

Several methods have been proposed to overcome anti-CD38 interference in immunohaematology testing and to facilitate alloantibody screening, thus reducing the risk of
incompatible transfusions and the possibility of transfusion reactions. These include testing the patient’s plasma against a panel of reagent RBC treated with dithiothreitol (DTT) or trypsin. In addition, extended RBC phenotyping or genotyping of the patient prior to the first dose of daratumumab enables transfusion laboratories to provide RBC with a phenotype that matches the patient’s RBC phenotype, with the aim of preventing or at least minimising the risk of incompatibility, particularly when daratumumab interference cannot be immediately resolved and/or the RBC transfusion is urgent.6,14 Transfusion of phenotype- or genotype-matched RBC will also reduce the risk of sensitisation and future alloantibody formation.

DTT is a thiol-reducing agent that denatures RBC surface CD38 by disrupting the disulfide bonds in the molecule’s extracellular domain, therefore preventing anti-CD38 from binding to the RBC.6 The use of DTT treatment is a recognised immunohaematological method. The test is robust and reproducible6 but not automated, and it is primarily used by specialist or reference laboratories.

Trypsin is a proteolytic enzyme not routinely used in Australian laboratories and is less efficient than DTT treatment at cleaving cell-surface CD38.7 Other more commonly used proteolytic enzymes, such as papain, bromelin or ficin, are used in immunohaematology testing as part of antibody identification protocols, to enhance weak antibody activity or aid in the resolution of multiple antibody specificities. These enzymes may also be used as part of the immunohaematology laboratory tool kit for daratumumab interference investigations, but no validation studies of the use of these enzymes in the resolution of daratumumab interference have been published.

It must be noted that DTT and trypsin (along with other proteolytic enzymes) also denature or weaken the reactivity of some RBC antigens (see Box 1), and this should be taken into consideration when assessing results from tests where these agents are used. In particular, DTT is known to denature the Kell system antigens, and therefore, when used to resolve daratumumab interference, patients should be transfused with K-negative RBC unless they have been shown to be K-positive on previous testing.6 At present, reagent RBC pre-treated with DTT or trypsin are not available from reagent manufacturers. Australian laboratories may not have access to sufficient quantities of reagent RBC to prepare and maintain DTT- or trypsin-treated antibody screening or identification panels cells for regular routine use.

An alternative and the optimal approach to managing the interference of the anti-CD38 antibody would be to neutralise the anti-CD38 antibody in the patient’s plasma using soluble CD38 antigen or anti-CD38 idiotype antibody. However, both are expensive and not currently routinely available.

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**Box 1 Antigens denatured or weakened by treatment with DTT or proteolytic enzymes**

<table>
<thead>
<tr>
<th>DTT</th>
<th>Trypsin</th>
<th>Papain/ Bromelin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kell (K, k, Kp(^a), Kp(^b), Js(^a), Js(^b), Ku)</td>
<td>Cartwright (Yt(^b))</td>
<td>Duffy</td>
</tr>
<tr>
<td>Cartwright (Yt(^b))</td>
<td>Indian</td>
<td>Indian</td>
</tr>
<tr>
<td>Indian</td>
<td>JMH Ge(_2), Bp</td>
<td>JMH</td>
</tr>
<tr>
<td>Scianna</td>
<td>Ge(_3), Ge(_4), Ch/Rg</td>
<td></td>
</tr>
<tr>
<td>LW</td>
<td>Dombrock Xg(^a)</td>
<td></td>
</tr>
<tr>
<td>Lutheran</td>
<td>Bp(^a)</td>
<td>En(^{FS}) En(^{TS})</td>
</tr>
<tr>
<td>MER2</td>
<td>Ch/Rg Ge(_2), Ge(_4)</td>
<td></td>
</tr>
<tr>
<td>Ge(_3)</td>
<td>Xg(^a)</td>
<td>Fy(^a), Fy(^b), Fy(_6)</td>
</tr>
<tr>
<td>Dombrock</td>
<td>MN Yt(^a)</td>
<td></td>
</tr>
<tr>
<td>Some Diego</td>
<td>En(^{TS})</td>
<td></td>
</tr>
<tr>
<td>Cromer</td>
<td>Lutheran</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mer(_2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Knops</td>
<td></td>
</tr>
</tbody>
</table>

Cord blood cells do not bind anti-CD38 mAb. A suggestion has been made that these cells could be used, but manufacturers of reagent RBC are constrained by limited supply. In a routine transfusion laboratory, other sources of suitable cord blood samples would not typically be available and would require registration as an in-house in vitro diagnostic (IVD). In addition, cord cells have altered expression of some antigens, and this method is unlikely to be routinely offered by hospital or pathology laboratories.14,17

Obtaining an extended RBC phenotype for the patient prior to commencement of daratumumab therapy is important in the provision of phenotype-matched RBC for future transfusions. Knowledge of the phenotype means that donor RBCs negative for the common clinically significant RBC antigens that the patient lacks can be selected for transfusion, thereby reducing the possibility of RBC antibody formation.14 Patient RBC phenotyping should be performed by the transfusion laboratory prior to the patient commencing daratumumab and at least 3 months after any recent blood transfusion (which otherwise may lead to misleading results). The patient sample could be sent for genotyping where samples are unsuitable for phenotyping at any point pre- or post-commencement on daratumumab, but typing prior to treatment is recommended. The results are not received immediately, and this, in addition to antibody investigation confounded by the presence of daratumumab, might add to the delay in provision of safe blood for transfusion. Ideally, this information should be sought prior to commencement.
of treatment. As a minimum, the patient should be typed for Rh antigens, K, Jk, Jk, Fy, Fy and S, . To manage workload and preserve reagents used, phenotyping may be performed in regular, for example, weekly batches. Genotyping is currently only offered in Australia by the Australian Red Cross Blood Service in Brisbane. Rapid genotyping testing may be available, but routinely, a 1-week turnaround time should be taken into consideration.

A practical approach for immunohaematology testing of RBCs in myeloma patients receiving treatment with the anti-CD38 mAb, daratumumab, is detailed in the following section. The real-world constraints are discussed, recognising that investigations to resolve anti-CD38 interference are time consuming and labour intensive and may not be available to all laboratories, especially regional or rural laboratories.

**Pre-transfusion testing requirements**

**A: Prior to anti-CD38 therapy**

Clear and timely communication between the treating clinician, patient and transfusion laboratory is absolutely vital when anti-CD38 therapy is planned. Patients and healthcare providers must be made aware of the potential interference of anti-CD38 in pre-transfusion testing and of the potential sequelae if appropriate immunohaematological testing is not performed.

The transfusion laboratory can be provided with a request for phenotype if there has been no recent transfusion or RBC genotyping if the patient has been recently transfused or has a positive DAT, noting that the patient will receive anti-CD38 therapy. The clinician should provide the transfusion laboratory with a full and accurate transfusion, obstetric and drug history for the patient, and this may also require review of both hospital and laboratory records.

Routine pre-transfusion testing includes a blood group (ABO/RhD) and antibody screen and will establish pre-treatment baseline results. An RBC phenotype (or genotype) is most valuable and, as a minimum, should include: Rh (C, c, E, e), K, Jk, Jk, Fy, Fy and Ss antigens. Genotyping will be informative when phenotyping is not possible due to recent transfusion (i.e. in the last 3 months) or if the patient has a positive DAT or if suitable phenotyping reagents are not available. The RBC phenotype and genotype can assist the laboratory not only by suggesting what RBC alloantibodies the patient may potentially form but also by enabling transfusion of phenotype- or genotype-matched RBC, which will minimise the risk of RBC incompatibility in situations where underlying unexpected alloantibodies cannot be excluded in the presence of daratumumab. Furthermore, phenotype- or genotype-matched RBC transfusions will minimise the potential for sensitisation and future alloantibody formation. A clinical decision may be required on whether to limit or prioritise chosen phenotypes based on the urgency of the request and the difficulty of providing matched units for transfusion.

Information relating to the immunohaematology testing should be maintained in the patient’s clinical and laboratory files, and the patient should be provided with a ‘patient alert card’, which can inform healthcare providers that they are receiving anti-CD38 therapy. It is important to consider that patients may attend several hospitals and be tested at several transfusion laboratories, and it is also important to remember that in the absence of a jurisdictional or national alloantibody register, information about the patient’s treatment with daratumumab and RBC phenotype and prior RBC alloantibody history may not be accessible by the transfusion laboratory or hospital at which the patient currently presents.

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**Prior to treatment with daratumumab**

1. Communications from treating professional and transfusion laboratory to document that the patient is to start anti-CD38 mAbs.
2. Provide a full transfusion, obstetric and drug history.
3. Perform an antibody screen and DAT.
4. Perform an extended RBC phenotype (or genotype, where indicated).
5. Provide patient with an alert card (see Fig. 3).

**B: Following commencement of anti-CD38 therapy**

It is extremely important for the transfusion laboratory to know that a potential transfusion recipient is receiving anti-CD38 therapy. The treating clinician needs to understand the impact on pre-transfusion testing and to consider the timeframes for testing and provision of blood. Specimens from patients on anti-CD38 may need to be referred to a reference laboratory for the more complex investigations necessary in these cases. The resource impacts on specialised reference services would be mitigated if the neutralising antibody was listed on the Australian Register of Therapeutic Goods (ARTG) and available. This would also simplify and expedite pre-transfusion testing and improve the relative safety of transfusion.

The ABO/RhD typing is unaffected by the presence of anti-CD38 and can be reported normally. The anti-CD38 panagglutination typically results in a universally weak (1+ or 2+; using 0–4 scoring) positive antibody
screen. If one or more of the screening cells are strongly reactive (3+ or 4+), this suggests the potential presence of an antibody, possibly an alloantibody, other than anti-CD38 (Fig. 1).

To overcome anti-CD38 interference, the antibody screen can be repeated using DTT- or trypsin-treated reagent screening RBC. If this is negative, it may be assumed that no clinically significant RBC alloantibodies are present, with the caveat that specificities directed against antigens denatured by the chosen enzyme cannot be excluded. In the case where DTT-treated cells are used, the laboratory can select donor RBC that are ABO, RhD and K compatible, and these might be issued using the standard institutional cross-match (XM) protocol for a negative antibody screen, for example, electronic (computer) or immediate spin (IS) XM. In the absence of an identified RBC alloantibody using DTT-treated screening cells, the decision to provide more extended phenotype- or genotype-matched RBC beyond RhD and K (including Rh Cc, Ce, Jkα, Jkβ, Fyα, Fyβ and Ss) will be influenced by the availability of suitable units, clinical urgency of transfusion, anticipated current and future transfusion requirements and local policy. If the patient is revealed to have an unexpected genotype with potential antibody formation, this could be considered in planning.

Note that apart from DTT and trypsin, no validation studies have been published for other enzymes or methods for the purpose of resolving daratumumab interference. Thus, if other enzymes or methods are used, our consensus is that blood matched to the patient’s phenotype/genotype should be given, particularly if long-term transfusion support is anticipated.

A positive antibody screen using DTT- or trypsin-treated reagent RBC suggests that the patient has an additional RBC alloantibody. The antibody specificity will need to be determined using a DTT- or trypsin-treated RBC. Antigen-negative blood may then be selected for XM. RBC that match the patient’s extended RBC phenotype/genotype should be selected for transfusion, with the degree of matching determined by clinical urgency and the practicable availability of the desired phenotyped donor blood. A full IAT XM is required, but this will be incompatible unless DTT- or trypsin-treated donor cells are used for the XM.

The flowchart (Fig. 2) represents the expert group’s recommendation for pre-transfusion testing in the presence of anti-CD38. It is recognised that not all transfusion laboratories in Australia and New Zealand will either routinely use or have access to DTT- or trypsin-treated reagent cells. The scope of testing will depend on institutional policy, clinical urgency and availability of appropriately phenotyped (or genotyped) donor RBC. Antibodies developed by patients to antigens such as Dombrock, which are destroyed by DTT and without routine typing sera for donors or patients, will be missed. Clinicians need to pay careful attention for signs of acute or delayed haemolytic transfusion reactions in patients on daratumumab after any transfusion; the genotype might provide a clue where the phenotype is not available.

<table>
<thead>
<tr>
<th>Pre-transfusion testing following commencement of daratumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Provide laboratory with a full transfusion, obstetric and drug history.</td>
</tr>
<tr>
<td>2 Order a blood group (ABO/RhD) and DAT.</td>
</tr>
<tr>
<td>3 Perform antibody screen panel.</td>
</tr>
<tr>
<td>4 If panagglutination is indicative of interference with anti-CD38 mAb on the antibody screen (see Fig. 1), perform an antibody screen using DTT- or trypsin-treated screening cells. (Other enzymes, e.g. papain, bromelain, ficin, may be used as an adjunct to help identify or exclude particular alloantibodies to RBC (Note: Methods other than DTT or trypsin have been used but might not be validated for the purpose of resolving daratumumab interference. We suggest that if enzyme methods other than DTT or trypsin are used, then extended phenotype/genotype-matched donor RBC should be given (Rh Cc, Ce, Jkα, Jkβ, Fyα, Fyβ and Ss).)</td>
</tr>
<tr>
<td>5 Perform antibody screen panel.</td>
</tr>
<tr>
<td>6 Issue donor RBC.</td>
</tr>
</tbody>
</table>

C: Life-threatening bleeding and emergency transfusions

For patients experiencing life-threatening bleeding or in emergency situations where transfusion is required within 2 h, there may not be time for the recommended routine pre-transfusion testing. Previous antibody history, phenotype and genotype results are invaluable in this circumstance.

There is a need to balance the clinical risks of transfusion versus those of not transfusing the patient, but under no circumstances should transfusion be delayed in the setting of a bleeding emergency.

The greatest risk to the patient is transfusion of ABO-incompatible blood. In emergency situations, the risk is normally mitigated by transfusion of group O RhD-negative blood; however, it should be noted that RhD-negative blood is not necessarily the most appropriate in all cases, especially in patients that are Rh c-negative and or Rh e-negative. ABO and RhD typing are not affected by the presence of anti-CD38 antibody in the patient’s plasma.

Transfusions should be in accordance with institutional critical bleeding or emergency transfusion policies. Further information on transfusion in emergency situations...
can be found in the ANZSBT’s ‘Guidelines for Transfusion and Immunohaematology Laboratory Practice’.20

**Clinical considerations**

Daratumumab is the first anti-CD38 mAb that received clinic approval by the FDA in 2015 and subsequent TGA approval in Australia in 2017. Its use in combination with current therapeutics, such as lenalidomide or bortezomib, increases the frequency of minimal residual disease negative remissions in MM, which may translate to improvement in survival outcome.21,22 Healthcare providers have not been adequately prepared for the critical interference of this drug in laboratory tests, particularly pre-transfusion testing. The problem will increase if daratumumab’s use expands to early-phase disease treatment.

A crucial aspect in risk mitigation is education to increase awareness and a robust procedure to enable timely and routine communication with the blood transfusion laboratory. The patient and family members need to be aware of daratumumab’s interference in pre-transfusion tests and the potential impact this may have on any blood transfusions. A patient alert card (see Fig. 3) is also useful for this purpose. All levels of medical care – from nursing staff to doctors and transfusion laboratory

![Figure 1](image-url)
Figure 2 Pre-transfusion testing recommendations. *Refer to ANZSBT Guidelines for Transfusion and Immunohaematology Laboratory Practice; O-negative blood is not without risk and may not be suitable in all circumstances, e.g. patient has anti-c or anti-e antibodies; "Tests using DTT or trypsin treated red cells are published methods for resolving anti-CD38 (daratumumab) interference; however, testing may not be available in all laboratories and/or subject to regulatory restrictions; Extended phenotype/genotype including as a minimum: Rh (C, c, D, E, e), K, Jka, Jkb, Fya, Fyb and Ss; "Papain and bromeliad are not IAT methods for crossmatching purposes. DAT, direct antiglobulin test; DTT, dithiothreitol; IAT, indirect antiglobulin test.
scientists – need to be educated to ensure effective communication and adequate documentation in the patient record and the transfusion laboratory information system (LIS). Every public and private haematology/oncology facility should have a procedure to automatically notify the relevant transfusion laboratory when a patient is about to commence daratumumab and provide the appropriate specimens for testing. This will allow for baseline extended RBC phenotype (regardless of the immediate need for blood transfusion). The transfusions laboratory requires ongoing notification of daratumumab treatment when RBC transfusion is requested for up to 6 months post-treatment cessation. Updating blood transfusion requisition forms to include questions about antiCD38 mAb might be considered, as well as suitable alert notifications in electronic alert/chemotherapy

| ANTI-CD38 THERAPY OR PRETRANSFUSION (NON-URGENT CASES) | Prior to commencing anti-CD38 therapy, all patients should undergo blood group (ABO/RhD), antibody screen. If time allows, perform phenotyping or genotyping. Phenotyping should be performed if the patient has not been transfused in the preceding 3 months. Genotyping is recommended if the patient has been recently transfused or is DAT positive. |
| URGENT TRANSFUSIONS (Blood required < 2 h) | Issue blood using institutional protocols for emergency transfusion of Massive Transfusion Policy (MTP). |
| | • Emergency O RhD-negative RBCs. Refer to ANZSBT Guidelines for Transfusion and Immunohaematology Laboratory Practice. Transfusing O RhD negative blood is not without risk, and may not be suitable in all circumstances, e.g. if the patient has anti-c or anti-e antibodies. |
| | • Switch to ABO/RhD and Kell compatible RBCs where appropriate. |
| | Take samples before transfusion for retrospective testing and cross matching. |
| NON-URGENT TRANSFUSIONS | Complete blood group (ABO/RhD) and antibody screen, phenotyping or genotyping as per “Prior to commencing anti-CD38 therapy” box. |
| | Perform a routine IAT antibody screen. If negative, proceed as per usual institutional protocol. If positive, and the sample shows panagglutination typical of anti-CD38 interference, e.g. 1+ or 2+ reactions within all cells, then the sample should undergo testing using DTT or trypsin treated RBCs. |
| | Perform IAT antibody screen using trypsin treated RBCs. Tests using DTT or trypsin treated RBCs are published methods for resolving anti-CD38 interference, however, testing may not be available in all laboratories and/or subject to regulatory restrictions. If DTT or trypsin treated RBC testing is not available, provide phenotype compatible blood if available, or refer to a reference laboratory for further evaluation. Use of other routine laboratory tests, such as papain or bromelin, to exclude the development of a new existing alloantibody may assist in the selection process for phenotype compatible units. |
| | If DTT or trypsin treated RBC testing is possible, if negative, assume there are no clinically significant RBC antibodies, however, you cannot exclude antibodies to antigens denature by the chosen treatment method. Transfuse ABO/RhD compatible blood and blood compatible for any significant antigens destroyed by the method used, e.g. Kell compatible for DTT methods. Consider selecting blood matched to the patient’s extended phenotype or genotype, and particularly if long-term transfusion support is anticipated. Perform an abbreviated cross match (eXM or IS) and issue blood using the usual protocol. If an IAT crossmatch is used, note it will be positive unless donor cells are DTT or trypsin treated. If positive, this suggests that RBC alloantibodies are present. Identify these antibodies using DTT or trypsin treated ID antibody panel. This method cannot exclude alloantibodies against antigens denatured by the chosen treatment method. Select blood that is compatible for antibodies and antigens that are denatured by the chosen treatment method. If an alloantibody cannot be identified for any reason, consider selecting blood matched to the patient’s extended phenotype or genotype particularly if long-term transfusion support is anticipated. The extended phenotype and genotype should include at a minimum Rh (C, c, D, E, e), K, Jk*, Jk0, Fy* Fy and Ss. A full IAT crossmatch will be positive unless the donor cells are DTT or trypsin treated. |
prescribing systems and alerts in the transfusion LIS to state that the patient is receiving daratumumab.

In the transfusion laboratory, while both DTT and trypsin are widely recommended, these methods are not always practical when laboratories rely heavily on automation. These methods are manual and laborious and incur additional costs. Although robust and reproducible, in Australia, both DTT and trypsin used in these methods have not been approved for use as in vitro diagnostics by the TGA. There are no commercially available DTT or trypsin reagents listed on the ARTG, nor are DTT- or trypsin-treated reagent RBC screening or extended panels available. Thus, both methods would be considered ‘in-house’ methods and may not meet Australian IVD device regulations, despite being fully validated by laboratories before introduction. There is no current prospect of commercial availability of ATRG-listed soluble CD38 or anti-idiotypic antibodies to neutralise the effect of daratumumab.

In the face of these constraints, the default contingency for many laboratories will be to issue extended phenotype- or genotype-matched blood where available. The ensuing impact of increased demands on the ARCBS and the increasing need for relevant immunohaematology expertise outside of large metropolitan laboratories will need to be considered. The establishment of a national RBC alloantibody register has been under consideration and might reasonably include relevant documentation for these circumstances.

With respect to the impact on patients, the risk pertains not only to possibility of missing a significant alloantibody that may cause acute or delayed haematolytic transfusion reactions but also to the delay in issuing of blood products. The potential for delay is present both when transfusion laboratories are unaware that patients are receiving daratumumab and when, if aware, are required to undertake increased testing. Haemolytic transfusion reactions because of daratumumab interference with pre-transfusion testing were not reported in the two pivotal phase III CASTOR\textsuperscript{23,24} and POLLUX\textsuperscript{25,26} studies. The patients in these trials were in the relatively

Figure 3 Example of patient alert card.
early course of their disease (with a median of 1–2 prior lines of treatment) and were not commonly transfusion-dependent. Conversely, in the clinic, daratumumab is currently also FDA- and TGA-approved as monotherapy for heavily pretreated patients who have had at least three prior lines of therapy. It is, therefore, expected that higher transfusion requirements will be seen in these end-stage patients, and we cannot be certain of the notion that no haemolytic transfusion reactions have been observed in daratumumab-treated patients before. Clinicians and laboratories should be aware of the potential for acute and delayed haemolytic transfusion reactions and should investigate, document and report any such reactions, or adverse events through their local haemovigilance programme.

**Future directions**

As the use of mAb is becoming increasingly prevalent for therapy of cancers and other medical conditions, the concept of potential interference in critical laboratory tests needs to be recognised and appropriate antibody neutralising solutions developed, preferably prior to the widespread introduction of these agents into the community. The introduction of daratumumab into clinical use in MM has indeed created a predicament in the transfusion laboratory that is without precedent, but should serve as a case in point to gain experience and prepare for similar scenarios in the future. Any mAb that targets common antigens present on RBC have the potential to interfere with pre-transfusion testing. Currently, these include the other anti CD38 mAb, such as isatuximab and MOR202, both of which are undergoing clinical studies for the treatment of MM. While the nature of interference of these monoclonal antibodies is anticipated to be similar to that of daratumumab, this may not become clear until the drugs are more widely used. It is unclear whether there is concurrent development of an antidote to neutralise any of their interference in critical tests within the core laboratory. For daratumumab, neutralisation methods (soluble anti-CD38 mAb or anti-CD38 idiotype antibody) have been used successfully and are a fast and uniform way to deal with the interference. Such kits could attain IVD approval and reduce the need for labour-intensive testing within the transfusion laboratory. Cost has been a barrier, and currently, the only commercial kit available (DIRA; Sebia, Evry Cedex, France) is in use to resolve daratumumab’s interference in serum protein electrophoresis and immunofixation assays, which are methods to quantitate and type monoclonal immunoglobulins (M-proteins), respectively, in the serum or urine. In the absence of such a kit for pre-transfusion testing, other ways to resolve the problem, to minimise workflow disruption to transfusion laboratories and mitigate risks to patients must be considered.

If a transfusion laboratory is not aware that a patient is receiving daratumumab, protracted investigation and delays are likely to occur when unexpected panagglutination is found in the routine antibody screen. A national database (or register) of patients treated with daratumumab or any other mAb that interferes with pre-transfusion tests could provide an easily accessible source of information for patients who may demonstrate interference in immunohaematology testing. Such a database, if incorporated in an antibody register or database, could also potentially alert the local laboratory service when a patient is known to have RBC allo- or autoantibodies. This might reduce delays in immunohaematology testing and time to appropriate transfusion. Such databases have been recommended in other jurisdictions.

At the hospital level, routine and automatic notification to the transfusion laboratory about a patient’s treatment status could be mandated. Automated alerts, through electronic medical record systems to the transfusion laboratory, for every patient on treatment that may interfere with immunohaematology tests or require selection of specialised blood products could be implemented. Investment in the development of this infrastructure needs to happen now to prepare adequately for the surge of mAb in clinical use in the near future.

For future targeted therapies, we emphasise the need to explore fully any potential interference with critical laboratory assays that may impact the other areas of clinical practice prior to their introduction into the clinics.

**Acknowledgements**

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**References**


Quach et al.


15 Branch DR, Muensch HA, Sy Siok Hian AL, Petz LD. Disulfide bonds are a requirement for Kell and Cartwright (Yta) blood group antigen integrity. *Br J Haematol* 1983; **54**: 573–8.


CLINICAL-SCIENTIFIC NOTES

Benefit of routine testicular examination: hypogonadism in a person with 47XYY

This case study is to remind readers of the benefit of carrying out routine testicular examination in people who present for unrelated reasons. A 70-year-old Caucasian man presented with a 20-year history of type 2 diabetes, and treated with insulin for 15 years, after having his driver’s licence suspended due to poor compliance. The level of HbA1c was 102 mmol/mol and he was administering 60 units ‘NovoMix’ insulin in the morning and 50 units in the evening.

He had a history of a speech disorder, which he said was the cause of poor performance at school. He received speech therapy in his early 20s, which improved his speech greatly. The patient described himself as always being different to his classmates, and as somewhat of a loner. He had been an apprentice carpenter for 4 years, but had spent most of his working life as a public servant in an administrative capacity and was now retired. He was not able to tolerate alcohol, was a non-smoker, lived alone, had never had a partner or children and was homosexual. There was no history of macrovascular disease.

Libido had been low especially after a diagnosis of Burkitt lymphoma had been made 2½ years previously, with the patient receiving six cycles of DA-R-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide and rituximab).

On examination, the patient was tall with a height of 186 cm, a weight of 146 kg and a body mass index of 42 kg/m². He had asymptomatic peripheral neuropathy, mild non-proliferative diabetic retinopathy, bilateral cataracts, microalbuminuria (25 mg/mmol creatinine) but normal renal function (estimated glomerular filtration rate 86 mL/min). Testes were small in size measuring 6–8 mL, pubic hair was adult and there was no gynaecomastia.

Investigations confirmed primary hypogonadism with a low testosterone of 2.6 nmol/L and raised luteinising hormone of 22 IU/L and follicle stimulating hormone measuring 25 IU/L. Chromosomal analysis did not confirm Klinefelter syndrome, which seemed clinically likely, but rather 47XYY, a condition not usually associated with hypogonadism or small testes. The alkylating agent cyclophosphamide is the most likely chemotherapeutic agent responsible for adversely affecting the testes, with shrinkage of the gonads, and primary hypogonadism. The patient was given exogenous testosterone in the form of ‘Testogel’, with resultant increase in libido akin to how he had felt prior to receiving chemotherapy.

The patient had many of the features of XYY syndrome, a disorder, affecting perhaps 1 out of every 1000 males. Most people with this disorder are diagnosed serendipitously, as in this case, since apart from tall stature, there are no phenotypic features. The exact cause of error in cell division is not known. Intelligence is normal, but there is an increased incidence of learning disabilities, behavioural problems and speech disabilities, which benefit from speech therapy and tutoring. Aggression is not a feature, and fathering of children is the norm.

In summary, this unusual case demonstrates three points. First, routine testicular examination may reveal otherwise unsuspected conditions, which may also be treatable. Second, the diagnosis of XYY, as is so often the case, was unexpected, and third, some chemotherapeutic agents are toxic to the testis. A PubMed search for ‘value of routine testicular or scrotal examination’ produced a total of 45 citations, most relating to infertility and none similar to our case.

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References


Boerhaave syndrome: a common manifestation of a rare disease

A 65-year-old woman with multiple cardiovascular risk factors presented with sharp central chest pain, which radiated to the back and was exacerbated by inspiration and lying supine, and relieved by leaning forward. The patient also reported six episodes of diarrhoea on the day before presentation and one episode of vomiting. Chest X-ray revealed congested lungs and small bilateral pleural effusions suggesting cardiac failure or fluid overload.

She was admitted and investigated for acute coronary syndrome complicated by cardiac failure. However, serial troponin assays were negative, while white cell count was elevated and her pain persisted, prompting further investigations for an underlying cause. A computed tomography of the abdomen revealed lower mediastinal free gas in a pattern suggestive of a ruptured oesophagus (Fig. 1). The patient was subsequently airlifted to a tertiary centre, where she underwent a thoracotomy, debridement and drainage of mediastinum and a laparotomy for insertion of feeding jejunostomy. At the time of surgery, an adjacent oesophageal diverticulum was identified. Post-operative gastrografin swallow confirmed the ongoing presence of an oesophageal leak.

The leak was managed conservatively. The patient underwent an extensive inpatient stay followed by a period of rehabilitation. She has since been able to be recommenced on a normal diet and has made a full recovery.

More than half of oesophageal perforations are iatrogenic, such as following endoscopic instrumentation, while approximately a third are spontaneous in nature.1 Spontaneous oesophageal rupture, also known as Boerhaave syndrome, is attributed to barogenic trauma due to an increase in intraoesophageal pressure, typically during vomiting.2 It is a rare yet potentially life-threatening condition with a mortality rate as high as 50% if delays in diagnosis and treatment are incurred.3 Therefore, early diagnosis of oesophageal rupture is critical.

Spontaneous oesophageal rupture classically presents with a triad of symptoms including vomiting, chest pain and subcutaneous emphysema, known as Mackler triad. However, the combination of symptoms is not always present. The typical presentation includes chest pain, while shortness of breath, vomiting and other non-specific features are common.

Cases of oesophageal perforation are most frequently associated with raised intraluminal pressure, such as in vomiting or retching. However, compromised oesophageal wall integrity, such as in chronic reflux,4 eosinophilic oesophagitis5 and dermatomyositis6 have also been identified as potentially important predisposing factors. Our patient was eventually found to have an oesophageal diverticulum. As far as we are aware, spontaneous rupture with underlying diverticulum has not previously been described. It is unclear whether oesophageal diverticulum predispose to spontaneous rupture, but it is feasible that both may represent a weakness in the oesophageal wall.

This case illustrates the importance for clinicians to have spontaneous oesophageal rupture as part of their differentials when managing patients who present with chest pain.

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Figure 1 Computed tomography of the abdomen, soft axial. Arrow indicates lower mediastinal free gas.
Role of radiotherapy in management of gingival infiltration of chronic myelomonocytic leukaemia

Chronic myelomonocytic leukaemia (CMML) is a malignant haemopoietic stem cell disorder with clinical and pathological features of both a myeloproliferative neoplasm and myelodysplastic syndrome.¹

Gingival infiltration is a presenting symptom in 5% of patients. It is commonly seen in acute monocytic leukaemia.²⁻⁴

A 67-year-old woman presented with 18 months history of CMML and 15 months of leukaemic gingivitis. She had been treated with chemotherapy (oral thioguanine and azacitidine) due to moderate tumour burden and splenomegaly. White cell count and splenomegaly improved.

However, gingival infiltration progressed, as did associated symptoms: oral discomfort and bleeding, anorexia, nausea and 10 kg weight loss. Bleeding did not respond to tranexamic acid (Fig. 1).

She was treated with low-dose palliative radiotherapy 4 Gy in two fractions⁵,⁶ to entire oral cavity without acute or late toxicity. There was gradual response such that by 12 weeks post radiation there was resolution of oral discomfort and anorexia, reduced bleeding, and 75% reduction in gingival hypertrophy (Fig. 2).

Response was maintained for further 7 months. She was treated with further 4 Gy in two fractions to the oral cavity but died 6 weeks after from disease progression.

Gingival hyperplasia is characterised by progressive enlargement of the interdental papilla as well as the marginal and attached gingiva. Mucosal haemorrhages, ulcerative gingivitis, infectious gingivitis and odontalgia may be observed.

Dental caries and poor oral hygiene have not been described as risk factors, however, they can predispose to superinfection, necrosis, pain and bleeding.

Figure 1 Pre radiotherapy.

Figure 2 Twelve weeks post radiotherapy.
Letters to the Editor

Generally, gingival hyperplasia resolves completely or at least partly with effective chemotherapy. Low-dose radiation has been shown to be an effective treatment with minimal morbidity in the setting of indolent non-Hodgkin lymphoma. In the event of failure of response of leukaemic gingivitis to chemotherapy, palliative low-dose radiation can be used for local symptom control. It is likely to be effective and well tolerated with minimal toxicity.

References

Encephaloclastic cyst: a rare complication of a malfunctioning methotrexate Ommaya reservoir

The Ommaya reservoir (OR) is an intraventricular catheter system used to treat leptomeningeal malignancy. It allows for the instillation of chemotherapy into the cerebrospinal fluid (CSF) providing consistent drug levels. Methotrexate (MTX) can be administered intrathecally to treat leptomeningeal metastases. Known neurotoxicities include aseptic meningitis, seizures and polyradiculopathy. Encephaloclastic cysts are non-infectious complications rarely seen in the OR resulting from the cystic dilatation of the brain parenchyma around a catheter in response to a chemotherapeutic agent. These cysts have been seldom reported and are believed to result from extravasation or back-flow of CSF along the catheter.

A 67-year-old woman with breast cancer carcinoma-tous meningitis developed confusion, drowsiness and left-sided hemiplegia 3 days after instillation of 12 mg MTX through her OR. The device was inserted 1 month previously, through the right frontal cortex and had four prior instillations (45 mg MTX total) without any reported complications. There was no trauma to the device and review of chemotherapy records showed no untoward events. Her magnetic resonance image (MRI) showed a cystic fluid collection, 24 mm × 16 mm × 27 mm in the right sub-cortical matter below the superi- or frontal gyrus with extensive white matter increased signal change with sulcal and ventricular effacement, as shown in Figure 1, with no enhancing focus.

Treatment included high-dose intravenous dexametha-sone, with subsequent removal of the OR and intraven-tricular catheter. During surgical removal, CSF sampling showed a pleocytosis consistent with aseptic meningitis. White cell count: 44, protein: 237 mg/L (0–400 mg/L), glucose: 4.0 mmol/L (2–4 mmol/L), culture negative. A biopsy of the cystic lesion showed inflammatory change with reactive gliosis and some haemorrhage; no evidence of malignancy was found. There was no eosinophilic infiltration or features of demyelination to suggest an immune reaction to the catheter. Testing of the removed OR ex vivo demonstrated a small leak from the underside of the reservoir, suggesting needle penetration through the base of the reservoir. One week later, her left-sided weakness and confusion began improving allowing for commencement of rehabilitation. A 1-week progress MRI showed regression of oedema and reduction in the cavity size to 18 mm × 10 mm. Her dexamethasone was weaned and she returned home independently after 20 days.

MTX CNS toxicity results from the disruption of the blood–brain barrier leading to focal necrotising changes and subsequent development of local chemical

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Encephaloclastic cyst: a rare complication of a malfunctioning methotrexate Ommaya reservoir

The Ommaya reservoir (OR) is an intraventricular catheter system used to treat leptomeningeal malignancy. It allows for the instillation of chemotherapy into the cerebrospinal fluid (CSF) providing consistent drug levels. Methotrexate (MTX) can be administered intrathecally to treat leptomeningeal metastases. Known neurotoxicities include aseptic meningitis, seizures and polyradiculopathy. Encephaloclastic cysts are non-infectious complications rarely seen in the OR resulting from the cystic dilatation of the brain parenchyma around a catheter in response to a chemotherapeutic agent. These cysts have been seldom reported and are believed to result from extravasation or back-flow of CSF along the catheter.

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MTX CNS toxicity results from the disruption of the blood–brain barrier leading to focal necrotising changes and subsequent development of local chemical
We report an unusual presentation of local toxic encephalitis due to a malfunctioning OR. Clinical features of confusion and hemiplegia prompted concern relating to device malfunction, with expedited reservoir removal and corticosteroids resulting in neurological recovery. Clinicians should consider MTX toxicity and device...
malfunction in patients who receive intrathecal treatment. Awareness to the possibility of device malfunction including early clinical review and imaging post instillation of chemotherapy through the OR may be beneficial to detect early complications.

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References


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**General correspondence**

**Time of administration of treatment for hypertension in renal patients**

Wang et al.\(^1\) make a valuable contribution to an aspect of blood pressure management often ignored. In 1961, in blood pressure studies over 24 h, we observed blood pressure did not fall at night in patients with malignant (accelerated) hypertension who had renal failure or were at risk of this.\(^2\) Wang et al.\(^1\) now provide a meta-analysis of subsequent studies and support our suggestion that ‘non-dipping’ hypertension is important in the generation of morbidity, and that evening administration of medication may be optimal. Their conclusion from the analysis is that evening dosing, when contrasted with morning administration, improves two surrogate markers of long-term benefit: restoring ‘dipping’ in ‘non-dipping’ hypertensives and decreasing urinary albumin. Information on renal function was provided in only two of six studies, totalling 138 patients. There was no significant change in kidney function when measured, but there was no information on the rate of progression of renal dysfunction. The studies did not follow patients for long enough to evaluate ‘hard’ endpoints, death and dialysis, and longer follow-up might have demonstrated renal function benefit from evening dosing. Another surrogate marker of prognosis in chronic kidney disease, urinary albumin excretion (UAE), was reported in only one study included in this meta-analysis. A reduction in UAE with evening dosing was highly correlated with the decrease in nocturnal blood pressure and with the increase in diurnal/nocturnal ratio of blood pressure but no rate of change in UAE was calculated.

Renal function is usefully considered as the rate of deterioration. Plasma creatinine, expressed as the reciprocal of plasma creatinine, or the estimated glomerular filtration rate, often demonstrates linear progression, allowing calculation of rates of deterioration in individual patients. Future studies could usefully record more frequent measurements of plasma creatinine and UAE in each individual and identify those responding to changes in time of administration. Time series analysis, utilising Bayesian statistics with Kalman Filtering, were developed for my group to monitor progression of renal function and to detect and evaluate the probability of change.\(^3\) If this method is utilised in any prospective trial of change in administration time (or retrospectively if enough data points are available) many fewer subjects will be needed to confirm or refute the conclusions of this meta-analysis.

My personal clinical experience provides examples of a change in the rate of progression of kidney failure in some patients when there were therapeutic changes to modify nocturnal blood pressure, I have proposed\(^1\)\(^2\) that in the clinic records of renal function and of urinary albumin/creatinine ratio should be considered...
Starting beta-blockers during exacerbations of chronic obstructive pulmonary disease

We read the report of Neef et al. on the safety of starting beta-blockers during exacerbations of chronic obstructive pulmonary disease (COPD) with interest.¹ We have also been concerned about the high risk of adverse cardiac events during COPD exacerbations and whether beta-blockers can offer cardioprotection for such patients. We recently undertook a prospective study to test the feasibility of starting a cardioselective beta-blocker in patients admitted with exacerbations.² We stopped recruitment after screening more than 570 patients but only managing to enrol 23 (the reasons for exclusion are listed elsewhere²). Of these 23, only 16 completed 3 months treatment and only 12 reached the target dose of 95 mg metoprolol daily. Symptomatic hypotension was a frequent problem leading to two withdrawals and two failures to attain the target dose. Half of those recruited experienced at least one serious adverse event, including eight who were readmitted with further COPD exacerbations.

The finding that beta-blockers were better tolerated in Neef et al.’s retrospective study suggests that there was some selection bias and their reassuring observations may not be generalisable to a wider COPD population. It would be interesting to know if their patients continued to tolerate the beta-blocker after discharge. Patients with severe COPD are a particularly vulnerable population. Hypotension (observed in both Neef et al.’s and our study) and an increased risk of falls could have disastrous consequences. However, we do agree with regard to the respiratory safety of cardioselective beta-blockers: none of the patients in our study had a significant deterioration in lung function after starting the beta-blocker. Cardioselective beta-blockers do not appear to have acute effects on airway calibre in COPD.³

Although the retrospective evidence suggests that cardioselective beta-blockers are probably safe, there is still no prospective evidence on the balance of risk and benefits in COPD patients. An American study is currently recruiting patients to see whether beta-blockers reduce the risk of COPD exacerbations⁴ and we are planning a study in Australia and New Zealand to assess the cardioprotective effects of beta-blockers in COPD patients. Until the evidence from these trials becomes available, we suggest that beta-blocker therapy is reserved for those with clear cardiovascular indications and that these patients are monitored carefully for adverse effects.

References


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Author reply

We thank Hancox and colleagues1 for their interest in our recently published paper.2 Our study of beta-blockers started during admission with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) demonstrated that these drugs appeared to be well-tolerated.2 In contrast, the feasibility study reported by Chang, Hancox and colleagues highlighted these authors’ difficulties in recruiting for a prospective study of beta-blockers commenced in a similar context.3

Although we acknowledge the limitations of our retrospective study, our detailed review of 36 patients in whom beta-blockers were initiated during AECOPD (see table 1, online supplement*) found they were generally safe. Our study included patients with severe airflow obstruction, as well as those with significant bronchodilator response. It is reassuring that respiratory adverse effects were not prevalent in either our own study or in the prospective study of Chang et al.3 Unfortunately, given our study was a retrospective audit, we were unable to assess the long-term tolerability of beta-blockers in this cohort. Collection of such information in prospective trials will be critical to determining the utility of commencing beta-blockers in patients with chronic obstructive pulmonary disease (COPD).

We concur with the opinion of Hancox and colleagues that cardioselective beta-blockers should not be withheld in patients with COPD and clear cardiac indications for their use, and our data suggest continuation of beta-blockers in patients admitted with respiratory illness is appropriate. We recently highlighted the prevailing perception among clinicians that beta-blockers are contraindicated in COPD through our finding that only 44.8% of patients with AECOPD and clear cardiac indications for beta-blocker therapy were found to be receiving beta-blockers.4 Unpublished data from this same cohort of 1071 patients with AECOPD demonstrated significant rates of in-hospital cardiovascular events, including atrial fibrillation with rapid ventricular response (100 patients, 9.3%) and acute coronary syndrome (43 patients, 4.0%) occurring in the total cohort. Furthermore, our data suggest a statistically significant increase in rates of atrial fibrillation with rapid ventricular response following the cessation of beta-blockers during admission compared to those in whom they were continued throughout the hospital admission (Table 1).

To address these issues further, we are conducting a prospective study of the safety and tolerability of initiating beta-blockers during AECOPD in patients with clear cardiac indications.3 While beta-blocker use is associated with reduced rates of AECOPD in numerous observational studies, it is unclear if this is due to a direct effect on COPD or due to improved medical management of concomitant cardiac disease.5,7 Our study will include only patients with indications for beta-blocker use for which mortality benefit is unequivocal. It remains to be seen whether feasibility and tolerability mirror or differ from those reported by Chang et al., and we look forward to presenting these results.

Table 1 Univariate analysis of risk of cardiovascular events following cessation of beta-blocker therapy compared to those in whom it was continued throughout admission.

<table>
<thead>
<tr>
<th></th>
<th>Beta-blockers ceased</th>
<th>Beta-blockers continued</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation with rapid ventricular response</td>
<td>10/23</td>
<td>13/253</td>
<td>14.2 (5.24–38.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0/23</td>
<td>9/253</td>
<td>0</td>
<td>0.62</td>
</tr>
</tbody>
</table>

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Iron polymaltose infusion therapy during pregnancy

We read, with interest, the article by Grzeskowiak et al. on optimising intravenous (i.v.) iron dosing in pregnancy. The authors recommend dosing according to adjusted pre-pregnancy body weight and caution against the unknown harms of excessive i.v. iron resulting in adverse pregnancy outcome. The practical problem in implementing the recommended dosage is the non-availability of the pre-pregnancy bodyweight to clinicians at treatment centres administering iron infusion. We describe an alternative approach using a simpler dosing model based on the patient’s haemoglobin level, but capped at 1000 mg.

In our outpatient clinic, 105 pregnant women received iron infusions between 2014 and 2017; 33 received the infusion in the second trimester and 72 in the third. Their haemoglobin (Hb) level ranged from 84 to 130 g/L and the ferritin level ranged <8–30 μg/L.

Dosage schedule: 150 mg of iron polymaltose to raise Hb by 10 g/L, aiming to bring the patient’s Hb level to 130 g/L, plus 200–500 mg to replenish the iron stores. The minimal dose was 500 mg and the maximum 1000 mg. The infusion was given over a 2-h period.

The treatment was very well tolerated with minimal side-effects in a small number of patients: (i) brief vasovagal episode (4), (ii) minor gastrointestinal symptoms (10) and (iii) mild arthralgia/myalgia (4).

Our experience suggests that capping the dose at 1000 mg can achieve an effective and adequate response in most of the patients and precludes overdosing and the possible ‘unknown harms’ discussed by Grzeskowiak et al.1

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References

**Clinical need for standardised multidisciplinary meeting assessment processes**

We read with interest the article by Johnson et al. regarding the development of a peer-review framework for cancer multidisciplinary meetings (MDM). MDM are a critical component of multidisciplinary oncological care, associated with improved patient outcomes and satisfaction, trials recruitment and interdisciplinary communication. While national and international guidelines exist relating to the conduct of MDM, processes still vary within and across institutions, differing in MDM frequency, the patients presented, team membership, leadership and communication. There is currently no standardised process within Australia to monitor the quality of MDM across different institutions and regional settings. However, variations between MDM may affect quality of care.

We recently reviewed neoadjuvant chemotherapy delivery for muscle-invasive bladder carcinoma (MIBC) in a metropolitan and regional setting and found MDM discussion to be a determinant of patients receiving neoadjuvant chemotherapy. Neoadjuvant chemotherapy is a standard of care for patients with MIBC. Our retrospective audit analysed 19 metropolitan patients and 23 regional patients who underwent radical cystectomy for MIBC. Regional patients had significantly lower rates of both referral to a preoperative MDM (84 vs 42%, \( P = 0.023 \)) and neoadjuvant chemotherapy (42 vs 13%, \( P = 0.043 \)). Nine of the 11 patients (82%) who received neoadjuvant chemotherapy had been discussed at a MDM, demonstrating the association between MDM and neoadjuvant treatment. There were no significant differences identified in the patient populations or type of chemotherapy. Optimising the MDM processes could therefore improve delivery of standard of care treatment for these patients.

While it is intuitive to believe that an MDM that meets regularly, with well-considered terms of reference, strong leadership and good team communication will make better decisions, there is minimal literature comparing variations or interventions in MDM processes and their effect on patient outcomes. Lamb et al. demonstrated that use of a checklist during MDM discussion to ensure adequate information was presented and all team members’ views discussed, improved efficiency and treatment decisions. There was no measure as to whether this translated into improved patient outcomes. The MDM peer-review framework described by Johnson et al. is another tool, designed to reduce variation in practice and provide opportunity for quality improvement. It may be limited by the labour-intensive process and the perceived relevance of its recommendations.

We strongly support ongoing research into improving the quality and efficiency of the MDM process. We argue that for any MDM intervention, improved patient outcomes should be the primary measure of success. While a peer-review process enables assessment of communication and leadership within an MDM team, we wonder whether less costly strategies should be explored first. Our research would suggest that process to ensure that all patients are discussed at an MDM soon after their diagnosis, which are attended (either in person or via teleconference) by all appropriate specialists, would be a welcome first step. It would be interesting to investigate whether a simple checklist used during the MDM to prompt discussion could further improve patient outcomes.

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References

6 National Cancer Action Team. *The Characteristics of an Effective*
Author reply

The response from Yau et al.1 to our article describing a peer review framework for multidisciplinary team meetings (MDM)2 is consistent with that provided during our study.3 In interviews with five peer reviewers and 17 multidisciplinary team (MDT) members in our study, it was acknowledged that peer review may be an effective vehicle for ensuring that MDM are conducted effectively but was resource intensive. Participants concluded that it might be more beneficial to identify how consistently MDM decisions reflected the clinical practice guidelines (CPG) and that patient outcomes may be a better measure of the effectiveness of MDM. Given the high cost of running MDM,4 it is imperative that they are efficient and effective.

In view of this feedback, we examined the adherence of breast MDM recommendations to CPG and of treatment to guidelines and MDM recommendations. In 1028 women with breast cancer (carcinoma in situ and invasive breast cancer), MDM recommended guideline-adequate treatment in 98.6% of cases. MDM recommendations were implemented for 89.7% of patients and 90.4% received guideline-adequate treatment. Patient preferences (n = 81), physician decision outside MDM (n = 8) and comorbidities (n = 7) were the main reasons for deviation from CPG.3

Yau et al. observed that variations in membership and leadership of MDM can affect the quality of their work. Indeed, variability in MDM dynamics resulting from variation in team composition was noticed by the peer reviewers observing the video recordings of MDM in our study. One MDT requested that an additional video recording be reviewed because several MDT members were absent in the initial video.3

We agree with Yau et al. that improved patient outcomes should be the primary measure of success of any healthcare. While improved outcomes for people discussed at MDM have been demonstrated,6–8 this research is subject to multiple biases.9,10 Given the difficulties associated with demonstrating a causal relationship of MDM on patient outcomes, trying to establish the effect of particular aspects of the MDM on outcomes is likely to be problematic.

Research suggests that one of the most effective methods of improving the quality of care is to monitor processes and patient outcomes (including patient reported outcomes) and to provide regular feedback against standardised benchmarks.11,12 The process of monitoring and providing feedback is growing in favour with health administrators and policymakers as clinical data collection and methods of manipulating data become more efficient. A movement towards ‘value-based’ healthcare13 is the impetus for many health services to monitor outcomes to promote care that is consistent with best practice guidelines and to reduce variability. Such an approach may be cost-effective and provide the requisite motivation for MDT to monitor their own performance and to address concerns about the quality of care.

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References

Corrigendum

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


The name of the author Adrian A. Y. S. Lee should be Adrian Y. S. Lee.

The authors of the article should thus be:

Penny Allen, Lucy Gately, Patricia Banks, Adrian Y. S. Lee, Garry Hamilton, Lavinia Tan and Sheryl Sim.

The authors apologise for the error.
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