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How technology is disrupting the health sector

Disruption and sustainable health care

Mental health of doctors

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EDITORIAL

Collaborative research between emergency medicine and physicians

Although emergency healthcare is a high-profile component of modern healthcare, the Internal Medicine Journal readers are unlikely to recall their Emergency-Medicine-resident terms with affection. The Emergency Department (ED) has long been plagued by noisy overcrowding, controlled ‘skating over thin ice’ chaos and a rapid conveyor stream of patients entering, being assessed and stabilised then waiting an eternity in the queue for admission or review. Juggling several patients at once takes some getting used to; multi-tasking out of necessity rather than a bored distractible sensibility is required to survive. Although emergency doctors cope well with undifferentiated illness and injury, taking a well-earned rest, meal or biological need break is often impossible.

The readership will baulk at long-buried nightmares of chaotically busy shift work wreaking havoc on their sleep–wake cycle and losing struggles to achieve a work–life balance. Most recoil at replays of fast-paced resuscitation of patients hanging on to life by a thread. The difficult caseload from abusive alcohol and drug-addled weekend binges, the sad and the mad, and being trapped within a sealed bubble of kinetic noise and intrusive interruptions remain challenging. Survival under stressful duress necessitates adaptive behaviours. An infamous tactic known to physicians is for emergency doctors to ‘turf and buff’ referrals to inpatient registrars who seem perpetually committed elsewhere, having grown roots in operating theatres or outpatient departments.

ED referrals signal more work, and no one wants that, more so towards the end of the working day. There is also that unspoken lack of trust in ED doctors assuming the mantle of ‘being the jack of all trades but master of none.’ We are seen as doers with a reflexive inclination to plasticise the airway and chest without hesitation. My editorial aspires to dispel the excitable resuscitator myth of the ED doctors among the Internal Medicine Journal audience. ED doctors are clear-sighted thinkers in crises and cooperative collaborators. Together, emergency and medical physicians battle to secure sick and injured people the best possible evidence-based patient journey towards a speedy recovery.

The difficult relationship we have had in coordinating and delivering clinical care from the ED to hospital admission and outpatient review thankfully is not the situation in research endeavours with our medical colleagues. There is grave concern about congested emergency health services from system-wide congestion.

The negative impact of growing demand, expanded scope of care and blocked access to inpatient beds has incited recent collaborative research between emergency medicine and our physician colleagues. The focus has been on processes such as medical assessment and chest pain units, short-stay units and ED geriatric/psychosocial/allied healthcare interventions. These measures reduce hospital overcrowding and congestion despite increasingly constrained hospital bed platforms and healthcare funding. There is now agitation for a whole-of-hospital approach to address patient flow bottlenecks, with enhanced movement of patients from emergency to inpatient critical care that underpin improved outcomes. These measures, now widely adopted by hospitals, have reduced lengths of stay from arrival to hospital discharge for improved patient journeys. Patients are more satisfied and the clinical outcomes are better with enhanced efficiencies and reduced costs.

Research collaboration between emergency medicine and medical specialties in Australasia has accelerated, perhaps as an unintended consequence of the imposition of National Emergency Access Target (NEAT) of 4 h length of stay before a patient is discharged or admitted from the ED. As NEAT compliance is highly associated with reduced patient mortality risk for emergency admissions, it behoves hospitals deliver patients requiring admission to wards best able to care for them, and as soon as possible. Scott et al. argue internally led clinical process redesign leads to superior and sustained improvements in ED access block. Furthermore, clinical redesign, team-based care and ED initiatives implemented internally improved NEAT compliance without incurring the risk of prematurely transferring unstable patients to inpatient wards. A time series analysis of hospital-wide performance at Sydney’s Royal Prince Alfred Hospital would not be possible without cooperation between ED and inpatient units.

Emergency medicine is not exclusively preoccupied with improving hospital and ED functioning at a systems level. The ED faces many disadvantages when it comes to controlled clinical trials. ED are chaotic frenetic high acuity care areas at the best of times; patients are unwell...
on presentation so informed consent is difficult. Emergency medicine focuses on rapid stabilisation and efficient diagnostication followed by timely exit from ED care. The jack of all trades and master of none ethos of emergency medicine militates against a more considered and in-depth research impetus. There are exceptions that have overcome these hindrances. A seminal toxicology study in 1995 showed gastric lavage to offer no additional benefit when added to activated charcoal in adults who had taken an overdose during 6 h of study observation. ED short-stay units could host controlled trials that assess for outcomes prior to 23 h after admission. Furthermore, emergency medicine researchers still conduct highly credible trials for our high volume presentations. For instance, intravenous (IV) fluids was found not to shorten recovery time for admitted adults who ingested excessive alcohol compared to no IV fluids, in a recent study.

On a more optimistic note, emergency medicine researchers have recently been involved in practice-changing collaborative cross-disciplinary clinical trials. Our specialty intersects with anaesthesia and intensive care medicine (in addition to being in the frontline for trauma care), with the trio of disciplines finding commonality in critical care interventions. Early administration of IV tranexamic acid improved mortality in major trauma care when ongoing bleeding is suspected. A recent high-impact clinical trial assessing the reputed benefits of early goal-directed therapy for septic shock has finally put early goal-directed therapy to bed. The PRISM Investigators, an international patient-level meta-analysis conducted by ED and Intensive Care Unit colleagues in Australia/New Zealand, the United Kingdom and the United States found no mortality risk reduction from aggressive haemodynamic management in adults suffering severe sepsis. PRISM and its Australasian Resuscitation in Sepsis Evaluation (ARISE) progenitor study represent a clarion call for emergency medicine’s aspiration to cross-disciplinary research with other specialties represented by the Internal Medicine Journal.

The Haemorrhage Alleviation with Tranexamic Acid-Intestinal System trial (HALT-IT) is currently assessing the clinical outcome of adults suffering acute gastrointestinal bleeding who were administered tranexamic acid in Europe, Africa and Asia. Surprisingly, HALT-IT is yet to engage a recruiting site in Australia or New Zealand. This represents an opportunity for Australasian ED and our gastroenterology colleagues to put their hands up for a high-impact definitive global study coordinated by the London School of Hygiene and Tropical Medicine.

Another promising avenue for collaboration is in clinical risk prediction for high-risk high-ED volume presentations. Working with academic cardiologists, emergency medicine researchers have developed safe and reliable risk stratification algorithms for patients with potential acute coronary syndrome. These widely promulgated guidelines are now incorporated into the latest iteration of the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand cardiology care guidelines. Now widely adopted in Australasian and New Zealand ED, patients with chest pain benefit from reduced admission and length of stay for risk stratification using ever more reliable serial cardiac enzyme assessment. The joint development of acute coronary syndrome risk stratification for patients presenting with chest pain to an acute care hospital represents an excellent model and successful precedent for research cooperation between emergency physicians and our physician colleagues. Let it be the start of the journey we take together.

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Our friend and colleague, Dr Paul Lee, passed away unexpectedly on 14 August 2017. Paul leaves an amazing legacy of brilliance and creativity.

Paul studied medicine at Melbourne University from 1996 to 2001. Between semesters, he took up a position as a Research Assistant in the Department of Biochemistry at the University of Hong Kong from 1997 to 1999. He was an intern in 2002 and a Junior Medical Officer in 2003 at the Royal Melbourne Hospital, where he undertook his Basic Physician Training in 2004–2005.

He performed the first year of Endocrine Training at Concord Hospital, Sydney, in 2006. He undertook the second year at St Vincent’s Hospital, Sydney. We were privileged to be his mentors for an extraordinarily productive PhD from 2008 to 2010 in the field of human brown fat physiology. He published eight first author papers in top-ranking journals, for which he was awarded the Garvan Institute Thesis Prize.

After submission of his PhD in 2011, Paul took up a Staff Specialist position in the Department of Diabetes and Endocrinology at Princess Alexandria Hospital and a Senior Lecturership at the University of Queensland. He garnered a prestigious post-doctoral fellowship from the National Health and Medical Research Council (2012–2014), which supported a fellowship at the National Institute of Health in Washington, generating another seven first-author top quality papers.

Paul returned to St Vincent’s Hospital and the Garvan Institute in 2014, where he took up the position of Group Leader, Brown Fat Physiology Group, in the Diabetes and Metabolism Division. Paul has been a mentor, role-model, supervisor, colleague and friend to over 20 advanced trainees and researchers over the last
4 years. Along the way Paul attained numerous scholarships, fellowships, grants and awards. Paul published close to 70 highly cited articles in leading journals. Paul’s studies have not only greatly contributed to the worldwide knowledge in human brown adipose tissue function, but also in bone health and diabetes.

In short, Paul was an amazing doctor, an excellent teacher and a superb researcher. He was a trailblazer whose generosity of spirit was matched by a humility that is lacking in health and academia. His death is a terrible loss for his family, his friends, his colleagues, the general endocrine and medical communities and his patients.

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CLINICAL PERSPECTIVES

Transcatheter mitral valve intervention: an emerging treatment for mitral regurgitation

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Key words
mitral regurgitation, transcatheter cardiac therapeutics, minimally invasive surgery.

Abstract
Mitral regurgitation (MR) is a valvular heart disease associated with significant morbidity and mortality. Transcatheter mitral valve intervention (TMVI) repairs or replaces the mitral valve through small arterial and venous entry sites and so avoids risks associated with open heart surgery. Transcatheter devices targeting components of the mitral apparatus are being developed to repair or replace it. Numerous challenges remain including developing more adaptable devices and correction of multiple components of the mitral annulus to attain durable results. The mitral valve apparatus is a complex structure and understanding of the mechanisms of MR is essential in the development of TMVI. There will likely be a complementary role between surgery and TMVI in the near future.

Introduction
Mitral regurgitation (MR) is a valvular heart disease that is associated with significant morbidity and mortality.1 Ten percent of persons aged over 75 have moderate or severe MR and 50% of patients with clinically significant MR are denied surgery due to risks associated with open heart surgery.2,3 When left untreated severe MR carries a 1-year mortality of up to 57%.4

Transcatheter mitral valve intervention (TMVI) repairs or replaces the mitral valve through small arterial and venous entry sites and so avoids risks associated with open heart surgery. TMVI can be offered to patients who are unable to tolerate open heart surgery. Several transcatheter devices are currently being developed worldwide. This article will discuss the basic science of MR and devices under trial in Australia for TMVI.

Anatomy
The mitral valve apparatus is comprised of an annulus, leaflets, chordae and papillary muscles (Fig. 1). The annulus is a D-shaped ring made of non-conductive fibrofatty tissue. The straight border abuts the aortic valve and forms a fibrous continuity known as the aorto-mitral...
curtain. The fibrous tissue expands at either edge of the curtain to form the left and right fibrous trigone.\textsuperscript{5,6}

The anterior leaflet forms one third of the annular circumference while the posterior leaflet comprises two thirds of the annular circumference. The two leaflets form a single continuous structure with the edge of the closure line referred to as the anterolateral and posteromedial commissures. The free edge of the leaflets is divided into lateral, middle and medial scallops termed A\textsubscript{1}, A\textsubscript{2}, A\textsubscript{3} and P\textsubscript{1}, P\textsubscript{2}, P\textsubscript{3} respectively.\textsuperscript{5,7}

The larger posteromedial muscle is typically supplied by a single dominant right coronary, and hence is more prone to infarction and rupture causing acute MR as compared to the smaller anterolateral muscle which typically has dual supply from the left anterior descending and left circumflex artery.\textsuperscript{9}

**Pathophysiology**

MR is caused by change in the structure or function of the leaflets, annulus or left ventricle. Chronic severe MR almost always involves change in the structure of all three components; however, the relative importance of each in the formation of MR is unknown. Biomechanical studies have proven that change in geometry of any of the three components leads to altered annular tension, resulting in annular dilatation and increased MR.\textsuperscript{9–12,14–16}

MR can be classified into degenerative MR (DMR) or functional MR (FMR). DMR is due to structural or degenerative abnormalities in the mitral valve apparatus (annulus, leaflets, chordae tendinae or papillary muscles). As DMR progresses, the pathology extends to the entire apparatus deforming the left ventricle, annulus, chords and papillary muscles.\textsuperscript{13} The prevalence of degenerative MR with mitral valve prolapse is around 2% and of this cohort 4% having severe MR.\textsuperscript{14} FMR occurs from a change in the mitral valve geometry secondary to ischaemic or non-ischaemic left ventricular dysfunction and in the absence of organic mitral valve disease.\textsuperscript{15} The two processes can coexist in the one patient and mixed forms of the disease are not uncommon. MR has been detected on transthoracic echocardiography in 50% of patients after myocardial infarction with 12% having severe MR.\textsuperscript{16} In a study of 470 patients with idiopathic dilated cardiomyopathy, 38% had moderate or severe MR\textsuperscript{17} The most common finding in DMR is mitral valve prolapse which encompasses a spectrum of connective tissue disorders including fibroelastic deficiency and Barlow disease. Fibroelastic deficiency occurs in patients typically over the age of 60 and has a relatively short clinical history. The pathophysiology is characterised by impaired production of connective tissue leading to rupture of one or more chordae but most commonly the middle scallop of the posterior leaflet (Fig. 1). The

**Figure 1** Mitral valve anatomy (A) Saddle shaped mitral annulus bounded anteriorly by aortomitral curtain (B). Anterior and posterior mitral valve leaflets (C). Barlow’s valve with thick, redundant bulky leaflets (D). Fibroelastic deficiency with ruptured chordae and prolapsed P\textsubscript{2} segment of the posterior mitral valve leaflet. Reproduced with permission from Zhu and Anyanwu and Adams.\textsuperscript{18}
affected leaflet may either appear normal or develop myxomatous changes with mucopolysaccharide accumulation. In contrast, Barlow disease is characterised by diffuse excessive myxoid tissue in multiple redundant leaflet segments along with chordal elongation and rupture and mitral annular dilatation (Fig. 1). Patients typically present under the age of 60 and have a longer history of MR.

In FMR, left ventricular pathology results in a secondary effect on the function of the mitral valve apparatus by causing papillary muscle displacement, leaflet tethering, annular flattening and enlargement. In ischaemic FMR, the consequence of left ventricular scar and remodelling results in local systolic tenting of the mitral valve with resultant MR in the presence of overall preserved left ventricular ejection fraction. Mitral annular dilatation occurs late in the pathophysiology and typically involves the posterior annulus. Non-ischaemic FMR, usually due to cardiomyopathy, is characterised by spherical left ventricular dilatation with concurrent symmetric mitral annular dilatation which reduces leaflet coaptation resulting in a posterior or centrally directed regurgitant jets. Acute MR may be due to infection causing leaflet perforation or spontaneous chordal rupture in degenerative valve disease.

### History, examination and diagnosis

Patients with chronic MR typically present with progressive dyspnoea over months to years. On clinical examination, there is a diminished S1, wide splitting of S2 and a holosystolic murmur best heard at the apex. In patients with mitral valve prolapse a mid-systolic click followed by a late systolic murmur is heard. Echocardiography is the cornerstone of the diagnostic evaluation of MR with qualitative and quantitative measures used to establish severity. Patients with a central jet >40% of the left atrium, vena contracta ≥0.7 cm, regurgitant volume ≥ 60 mL, regurgitant fraction ≥50% or effective regurgitant orifice ≥0.40 cm² are considered to have severe organic MR. In functional ischaemic MR, an EROA ≥220 mm² or an R Vol ≥ 30 mL identifies a subset of patients at increased risk of cardiovascular events. Both the pulsed Doppler mitral to aortic TVI ratio and the systolic pulmonary flow reversal are specific for severe MR (Fig. 2).

### Prognosis and treatment

MR begets MR. In both aetiologies, MR causes left ventricular volume overload resulting in chamber and annular dilatation thus increasing the severity of MR and worsening left ventricular size and function.

Patients with severe DMR may remain asymptomatic for years and only develop symptoms once LV systolic dysfunction occurs. In contrast FMR, where there is underlying LV dysfunction, often presents earlier with symptoms of congestive heart failure.

Mitrval valve surgery is recommended in patients with severe DMR and symptoms or without symptoms but evidence left ventricular dysfunction (left ventricular ejection fraction 30% to 60% or LV end systolic diameter > 40 mm). Mitral valve repair is preferred to replacement when surgically suitable. Symptomatic patients with chronic DMR, left ventricular ejection fraction <60% and who are not operable candidates should

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**Figure 2** Transthoracic echocardiographic assessment of MR (A) Colour flow Doppler demonstrating turbulent multicoloured regurgitant jet through the mitral valve (B). Continuous wave Doppler signal demonstrating rise and fall of MR jet velocity through the mitral valve with associated orifice area calculation. Reproduced with permission from The Department of Echocardiography, The Prince Charles Hospital, Brisbane, Queensland, Australia.
receive guideline directed medical therapy for left ventricular dysfunction, including angiotensin-converting enzyme inhibitors, β-blockers and aldosterone antagonists; however, there is little evidence demonstrating significant benefit of medical therapy in severe MR.23

In FMR, there are limited data to show that MR correction improves morbidity or mortality and as such only a Class IIb indication exists for surgical correction of secondary MR in severely symptomatic patients with persistent symptoms despite optimal medical therapy.23 All patients with functional MR and reduced left ventricular ejection fraction should receive guideline directed medical therapy for left ventricular dysfunction. Surgery is currently the gold standard treatment for MR. Correction of severe FMR at the time of concomitant surgery, for instance coronary bypass surgery, is often considered as standard care.25 Mitral valve repair is recommended in preference to replacement when prosthetic valve replacement is associated with low embolic risk but shorter durability whereas mechanical valve replacement has longer lasting durability but is associated with high risk of embolism necessitating lifelong anticoagulation.23

Unfortunately, a significant proportion of patients who need surgery are not operative candidates and up to 50% of patients with severe MR not being referred for surgery.1,13 Furthermore, mitral valve surgery can be associated with significant morbidity and mortality with one study of octogenarians reporting a mortality and morbidity rate of 17 and 35.5% respectively following mitral valve surgery.1,26 This has led to the development of TMVI as a treatment option for patients who are not surgical candidates.

Percutaneous valve intervention for mitral regurgitation

MitraClip system

Over the past few years, several technologies have become available as options for transcatheter mitral valve repair (TMVR) in patients with severe MR who are not surgical candidates. The largest clinical experience involves MitraClip system (Abbott Laboratories, IL, USA) (Fig. 3). The procedure involves placing the patient under general anaesthesia and the femoral vein is accessed via needle puncture and a delivery system inserted. A catheter is then advanced to the right atrium and under fluoroscopic and transoesophageal echocardiography guidance a trans-septal puncture into the left atrium is performed. A catheter is then advanced to the right atrium and under fluoroscopic and transoesophageal echocardiography guidance a transeptal puncture into the left atrium is performed. The trans-septal sheath is exchanged for a steerable guide catheter and dilator.
The clip delivery system is introduced into the guide catheter and the MitraClip device advanced into the left atrium. The clip is centred over the origin of the regurgitant jet and advanced into the left ventricle. Leaflets are grasped by clip arms and trapped between grippers and clip when the device is closed. Leaflet position and residual regurgitation is assessed at the time and if needed the clip can be re-opened and repositioned. If there is significant residual MR, often a second or even third device can be implanted. The MitraClip procedure is generally well tolerated even in patients with severe left ventricular dysfunction as compared to other types of TMVr.

Initial trials established the safety and feasibility of mitral valve repair using the MitraClip system in patients at high surgical risk with improvements in dyspnoea and low rates of procedure related adverse event and mortality. In the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II clinical trial a comparison was made to conventional surgery. Five-year data revealed the MitraClip system had higher rates of significant residual MR (12.3% vs 1.8%; \( P = 0.02 \)) and reoperation rates within the first 6 months (27.9% vs 8.9%; \( P = 0.003 \)). There was no difference in survival between the two treatment strategies.

The MitraClip system was approved by the US Food and Drug Administration in 2013 for patients with significant severe DMR who are at prohibitive risk for MV surgery.

**Edwards PASCAL mitral valve repair system**

The Edwards PASCAL system (Edwards Lifesciences, CA, USA) is a new TMVr system which employs mitral leaflet grasping to reduce MR. The system offers the following potential advantages: large implant size with spacer, long paddles facilitating grasping of the valve leaflets, independent leaflet clamping and minimal dependence on septal puncture height. Initial results in human trials have demonstrated percutaneous mitral repair with the Edwards PASCAL system appears safe and feasible. A prospective multicentre study has been initiated that will assess a composite end-point of all-cause mortality or recurrent heart failure hospitalisations and has an estimated primary completion date in July 2018.

**Cardioband annuloplasty**

The Cardioband device (Valtech Cardio, OrYehuda, Israel) involves a percutaneous direct annuloplasty that does not use the coronary sinus. The femoral vein is accessed and a catheter advanced into the right atrium. A transeptal puncture is performed through the delivery system enters the left atrium. The device is then delivered around the mitral annulus, secured in place through locking screws and tightened, thereby reducing the mitral annular circumference (Fig. 4). A multicentre feasibility study of the Cardioband device was conducted in 31 patients with functional MR. The Cardioband device was implanted percutaneously via the trans-septal approach under fluoroscopic and transoesophageal echocardiography guidance. It was successfully implanted in 29 patients, with no severe MR at the end of the procedure and 82% had ≤2+ MR at 30 days. There were 16 serious adverse events that occurred in nine patients including stroke, pericardial effusion, open heart surgery and renal insufficiency. The study demonstrated the feasibility and safety of percutaneous direct mitral annuloplasty with the Cardioband device in high-risk patients with MR.

**Carillon mitral contour system**

The Carillon device (Cardiac Dimension, WA, USA) is a metal rod with hoop-shaped helical anchors at either end (Fig. 5). Patients are sedated or anaesthetised for the procedure and the coronary sinus is cannulated from the jugular vein with a 9Fr delivery catheter. The distal anchor is deployed in the great cardiac vein and traction placed to plicate the mitral annulus and the proximal anchor then deployed. The degree of traction is assessed in the procedure using echocardiographic assessment and coronary angiography performed to ensure patency of the left circumflex artery that runs in close proximity to the great cardiac vein. Percutaneous mitral annuloplasty using the Carillon device was evaluated for safety and efficacy in a prospective, non-randomised, non-blinded trial in patients with symptomatic severe FMR. Of the 53 patients who were fully qualified, 36 underwent permanent device implantation, 17 had the device recaptured wither due to coronary artery compromise or failure to improve MR. At 12 months, MR and left ventricular volumes were significantly lower in the treatment group and exercise tolerance assessed with 6-min walk test was markedly improved in the implant patients.

**Tendyne valve**

The Tendyne valve (Tendyne Incorporated, MN, USA) is a trileaflet pericardial valve sewn onto a self-expanding nitinol frame with an atrial and ventricular fixation system tethered to the left ventricular apex. The procedure involves placing the patient under general anaesthesia and a left minithoracotomy is performed to gain access
to the LV apex. A guidewire, dilator and sheath are inserted sequentially through the LV apex to gain access to the left atrium. The valve is then advanced through the sheath and deployed in the left atrium. A polymer tether attached to the ventricular end of the device is then attached to the outer surface of the LV apex and used to position the valve in the native annulus and hold it in place (Fig. 6).

The first in-human transcatheter mitral valve replacement (TMVR) with the Tendyne valve was performed on two patients with severe degenerative MR in 2013. Immediately after deployment, MR, left atrial pressure and
pulmonary capillary wedge pressure were all significantly reduced. Both patients underwent subsequent mitral valve replacement surgery as per the study protocol and both Tendyne valves were explanted without any damage to the mitral valve, annulus or subvalvular structures.35

The Tendyne Early Feasibility trial recruited 30 patients with symptomatic MR (DMR or FMR) in a prospective, open-label, non-randomised trial to establish the safety and efficacy of the Tendyne mitral valve prosthesis. The primary end-points were MR grade < 2 at 90 days and freedom from cardiovascular death, stroke, myocardial infarction or surgery for valve related dysfunction.36 Successful device implantation was achieved in 28 patients (93.3%) with no acute death, stroke or myocardial infarction. Left ventricular volume had improved at 30 days and 75% of patients reported no symptoms at follow-up. In this small study the Tendyne mitral valve prosthesis appears to be a safe and effective therapy for patients with MR of either aetiology.36

Twelve Transcatheter mitral valve

The Twelve transcatheter mitral valve (Twelve Inc., CA, USA) is TMVR device being evaluated in a prospective, multicentre, non-randomised pilot study to establish safety and efficacy in patients with severe symptomatic MR who are not surgical candidates.37 It is composed of a self-expanding nitinol frame with a trileaflet valve composed of bovine pericardium. It has a fabric sealing skirt and requires transapical delivery. The primary outcome evaluated will be major adverse events at 30-days and secondary outcomes will be procedural success and MR reduction.

Valve-in-valve TMVR for degenerated bioprosthetic valves

Bioprosthetic mitral valves eventually degenerate and can require correction. Mitral valve reoperations are associated with higher mortality due to patient and procedure related factors.38 Valve-in-valve TMVR can spare patients the need for complex reoperation and experience in this technique is continuing to grow.

The advantage of bioprosthetic valve is the rigid structure with a fixed circumference making it an ideal target for TMVR. The TMVR size is easy to determine and cylindrical devices used for transcatheter aortic valve implantation can be used. Studies have demonstrated acceptable results in valve-in-valve TMVR with successful implantation, correction of mitral bioprosthetic valvulopathy and minimal post-operative complications.39–41 Traditionally, a transapical access was required but the majority of cases can now be undertaken through a transeptal puncture thus expediting patient recovery.
Unresolved issues in TMVI

Several concurrent unresolved technical issues exist which limit the clinical utility of TMVI. Potential limitations of percutaneous annuloplasty are that the coronary sinus only allows reduction of part of the annulus, technically stabilisation of material with enough force to obtain more than 20% diameter reduction is a challenge and proximity to the left circumflex artery with potential artery compression and ischaemia means non coronary sinus approaches are being investigated. Patients with long-standing MR often have a dilated annulus necessitating large delivery systems to deploy them. In some cases, the patient’s mitral apparatus cannot suitably accommodate the percutaneous valve, in particular, bulky TMVR devices are also prone to causing LVOT obstruction and CT planning is necessary to predict and prevent this occurring. TMVR does not completely eliminate MR and the degree of MR reduction required to obtain clinical benefit is unknown. Indeed assessment of the severity of MR after intervention is difficult due to multiple eccentric jets and artefact from the clips. TMVI is one of the more challenging cardiac interventions, and requires advanced imaging only available in a few centres and a longer learning curve which may limit its uptake. A plethora of devices exist aimed at percutaneously correcting MR and are currently under investigation. Results from initial animal and first-in-human studies are encouraging and it is likely that options will continue to grow and designs refined to improve outcome.

Conclusion

MR is a valvular heart disease that is associated with significant morbidity and mortality. The mitral valve apparatus consists of an annulus, leaflets and left ventricular attachments all of which contribute to mitral regurgitation. TMVI either through TMVr or TMVR is an emerging treatment modality for MR. Devices targeting components of the mitral apparatus are being developed in response to the burgeoning demand for this minimally invasive therapy. Numerous challenges remain including developing more adaptable devices and correction of multiple components of the mitral apparatus to attain durable results. There will likely be a complementary role between surgery and TMVI in the near future.

References


Electronic cigarettes in physician practice

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Key words
e-cigarettes, electronic cigarettes, harm reduction, nicotine dependence, smoking cessation.

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Abstract
There is growing evidence for the effectiveness of e-cigarettes as a quitting aid and, although not completely harmless, the scientific consensus is that they are substantially less harmful than smoking tobacco. More research is needed, but there is now sufficient empirical evidence and real-world experience over more than a decade to consider their use as a legitimate tobacco harm reduction tool for smokers who are unable or unwilling to quit with conventional strategies. Smokers should be advised that the highest success rates occur with daily use with nicotine e-liquid and newer e-cigarette models. After quitting smoking, it is preferable to aim ultimately to cease vaping if possible, but long-term use of e-cigarettes is safer than relapsing to smoking.

Ethical considerations
• Medical practitioners have a duty of care to provide the best possible management at each patient encounter. Withholding a legitimate treatment option that could prevent a life-threatening illness is a breach of that obligation.
• A policy that specifically allows the widespread sale and use of nicotine in its most lethal delivery system yet denies access to a far safer alternative is hard to justify on ethical grounds.
• Government interventions to restrict the rights and behaviour of individuals are not justified in the absence of evidence of material harm to others.

Introduction
Electronic cigarettes (e-cigarettes) were invented by a Chinese pharmacist in 2003 as an aid to quitting smoking. Their use has grown exponentially and they are now the most popular quitting aid in many countries. Currently, 1.2% of Australians aged 14 years and older use e-cigarettes (vape). Younger people try them mainly out of curiosity, whereas most adults use them as a less harmful alternative to smoked tobacco or as a short-term cessation aid.1

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Tobacco harm reduction
The main indication for e-cigarettes is tobacco harm reduction.2 The reality is that many smokers are unable or unwilling to quit with approved therapies in spite of repeated attempts to do so. Switching to vaping can satisfy the smoker’s need for nicotine and provides ‘a smoking experience’ without the vast majority of constituents in tobacco smoke which cause most of the harm to health.3

Conflicting views about e-cigarettes have arisen as research has lagged behind their rapid growth. According to the UK Royal College of Physicians, ‘it is important to promote the use of e-cigarettes, NRT [nicotine replacement therapy] and other non-tobacco nicotine products as widely as possible as a substitute for smoking’ although ‘they are not currently made to medicines standards and are probably more hazardous than NRT’.2 However, Australia’s National Health and Medical Research Council has taken a precautionary approach, stating that ‘further research is needed to enable the long-term safety, quality and efficacy to be assessed’.3 Nevertheless, smokers and ex-smokers are using these devices and physicians need to be informed to answer questions about them or advise on their use. This article provides an update on the latest evidence on e-cigarettes. It examines the indications for their use, their effectiveness for tobacco harm reduction, safety, legal issues and controversies. Finally, practical advice for their use by patients is presented.

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Nicotine has only relatively minor adverse health effects and harm from long-term exposure to nicotine is likely to be minimal. Nicotine acutely increases heart rate and blood pressure and may cause arrhythmogenesis and increased insulin resistance. Nicotine can impair foetal brain and lung development. There is some evidence in animal studies that nicotine can alter brain development in adolescents.

Harm reduction principles have been applied with success to other risky behaviours, such as long-term methadone for heroin users and clean needles and syringes to reduce the risk of HIV/AIDS in drug users. E-cigarettes now offer, for the first time, an affordable, well-tolerated reduced-harm product for smokers.

What are e-cigarettes?

E-cigarettes are battery-powered devices that heat a liquid solution (e-liquid) into an aerosol for inhalation, simulating the act of smoking. E-cigarettes are consumer products designed to replace another much more harmful consumer product, combustible tobacco. They are not marketed as pharmaceutical products or medical devices.

E-cigarettes consist of a battery, a vaporiser (heating element) and a reservoir for e-liquid. E-liquid consists of nicotine in varying concentrations (typically 0–3.6%) and flavourings dissolved in propylene glycol and vegetable glycerine. When the user breathes in or presses a button, the vaporiser is activated creating a fine mist for inhalation. Some of the aerosol is exhaled as a visible mist.

Early devices looked like cigarettes and are often referred to as ‘cigalikes’. Second- and third-generation models are larger, have more powerful, rechargeable batteries and refillable ‘tanks’ or replaceable cartridges of e-liquid. These models are more complicated to use but generally deliver more nicotine and are more satisfying (Fig. 1).

Vaping is considerably less expensive than smoking. This is an important consideration as smoking is increasingly concentrated in lower socioeconomic groups and causes considerable financial stress.

Are they effective for smoking cessation?

There is a growing evidence for the effectiveness of e-cigarettes as a quitting aid from changes in population

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<th>Electronic cigarettes</th>
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<th>Third generation</th>
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<td><strong>First generation (cigalikes)</strong></td>
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<td><strong>Larger refillable tanks</strong></td>
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<td>Resemble cigarettes</td>
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Figure 1 Electronic cigarettes.
smoking, observational studies, randomised trials and widely reported user experience.

The uptake of e-cigarettes has coincided with significant reductions in population smoking rates in many countries and it is likely that e-cigarettes are contributing to this.\textsuperscript{8,13} Millions of smokers report having quit using e-cigarettes.\textsuperscript{7,8}

Longitudinal studies using national survey data suggest that e-cigarettes are increasing quit rates. In the United States, Zhu \textit{et al.} found that smokers who used e-cigarettes were more likely to have successfully quit smoking for at least 3 months compared with non-users.\textsuperscript{9} In England, Beard \textit{et al.} reported that the increase in use of e-cigarettes was also associated with higher success rates of quit attempts.\textsuperscript{9}

The few randomised controlled trials tested early e-cigarette models which had poor nicotine delivery, but found similar efficacy to nicotine replacement therapy.\textsuperscript{10,11} Later-generation models deliver nicotine more efficiently and are likely to have higher quit rates.\textsuperscript{12}

Not all studies have shown a benefit. Some observational studies or meta-analyses of both observational and randomised studies have found no net quitting benefit. However, these studies suffered from limitations, such as selection bias, imprecise measures of frequency and duration of use, failing to indicate whether users were trying to quit and unmeasured confounders.\textsuperscript{11}

While anecdotal reports are not strong scientific evidence, the large number of individuals who have used e-cigarettes to quit smoking forms part of the evidence base.

\textbf{Safety}

Although further research is needed, there is very little evidence so far of serious harm from 10 years of real-world use and from studies up to 2 years.\textsuperscript{10} The most common adverse effects are irritation of the mouth and throat and dry cough, which tend to be mild and self-limiting.\textsuperscript{10}

The scientific consensus is that e-cigarettes are substantially less harmful than smoking. Like all new drugs or treatments, the long-term effects of vaping are not yet known.\textsuperscript{2} However, the Royal College of Physicians’ report concluded that the risk from long-term vaping is unlikely to exceed 5\% of the harm from smoking tobacco.\textsuperscript{2} As regular e-cigarette use is almost exclusively confined to smokers and ex-smokers, any risk should be compared to the considerable risks of continuing to smoke.\textsuperscript{6,15}

Almost all the harm from smoking is from the tar, carbon monoxide and other toxic chemicals caused by burning tobacco. As there is no tobacco or combustion in e-cigarettes, no smoke or products of combustion are produced. Some potentially harmful constituents are present in e-cigarette vapour, but at much lower levels than in cigarette smoke and in most cases below the levels known to cause harm.\textsuperscript{14}

Furthermore, there is a dramatic reduction in carcinogens and other toxicants measured in the blood and saliva of users compared to tobacco smokers.\textsuperscript{15}

A recent study estimated the cancer risk from vaping as less than 1\% that of smoking, based on levels of known cancer-causing agents reported in studies of e-cigarette vapour.\textsuperscript{16}

Indeed, many studies have found significant health improvement when smokers switch to vaping, including improved asthma, chronic obstructive pulmonary disease, blood pressure, cardiovascular health, lung function and reduced pneumonia risk.\textsuperscript{17–19}

Modelling studies show a net positive public health effect based on current estimates of the risks and benefits of vaping. A study by Levy \textit{et al.} estimated that up to 6.6 million premature smoking-related deaths could be prevented in the United States if most smokers switched to e-cigarettes over the next 10 years. Using pessimistic assumptions, an estimated 1.6 million deaths could be averted.\textsuperscript{20}

Potential health concerns of vaping include exposure to second-hand vapour, nicotine dependence and burns from malfunctioning batteries. The evidence is clear that the levels of toxicants in vapour are unlikely to pose any significant health concerns for bystanders in most situations.\textsuperscript{2} Dependence on e-cigarettes is less than for combustible cigarettes.\textsuperscript{2} Cases of e-cigarette batteries exploding or catching fire have been reported but are rare.

Diacetyl, a flavouring chemical in some e-liquids, has been linked to bronchiolitis obliterans, a serious, rare lung disease (‘popcorn lung’). However, levels of diacetyl are much lower in vapour than in tobacco smoke and there are no reported cases of the condition caused by smoking or vaping.\textsuperscript{21} High levels of formaldehyde were found in early laboratory tests, but subsequent studies have found very low levels when tested under realistic use conditions.\textsuperscript{22} Fine particulate matter is present in e-cigarette aerosol; however, its composition is very different to smoke particles and its toxicity is likely to be much less.\textsuperscript{2}

Electronic cigarettes are not currently regulated in Australia, raising uncertainties about safety, quality and labelling accuracy.

\textbf{Controversies}

A prominent issue raised is that vaping may entice young people who would never have smoked to take up smoking, the so-called ‘gateway’ effect. However, while young people may experiment with e-cigarettes, regular
use is almost exclusively confined to those who already smoke.23 Young people who try vaping are also more likely to try smoking, but there is little evidence of cause and effect. Furthermore, the great majority of young people who vape do not use nicotine e-liquid.24

Another concern is that vaping may undermine decades of tobacco control efforts to denormalise smoking by making smoking behaviour appear socially acceptable again. However, population studies show that the opposite effect appears to be occurring – uptake by never-smoking adults is rare and there is no evidence of long-term former smokers relapsing to smoking.13

A third concern is dual use (using an e-cigarette while still smoking). This could be important as any amount of smoking tobacco is harmful. However, evidence is emerging that dual use is frequently part of a transition phase to quitting for many smokers and dual users are more likely to quit than exclusive smokers.6 Furthermore, dual users smoke less intensely and most studies have demonstrated reduced biomarkers compared to smoking alone.23

### Use in Physician Practice

Smoking remains the leading cause of preventable illness and death in Australia.26 Physicians are confronted daily with people suffering from smoking-related diseases. Many patients will have tried to quit with approved therapies yet have failed repeatedly. Physicians have an ethical obligation to explore all strategies to improve health and switching to an e-cigarette is now a legitimate, evidence-based option for reducing harm.

Suggested guidelines for counselling patients on e-cigarettes are listed in Table 1.27

Patients should also be advised about the legal pathways for using e-cigarettes (Table 2).

### Conclusion

Electronic cigarettes are a valid alternative for smokers who have been unable to quit using the available first-line therapies. Evidence for effectiveness is growing and the scientific consensus is that they are substantially less harmful than smoking. Although more research is needed, there is now sufficient empirical evidence and real-world experience to consider their use as a legitimate tobacco harm reduction tool.

### Practice Points

- E-cigarettes are battery-powered devices that heat a liquid solution into an aerosol for inhalation and simulate the act of smoking.
- E-cigarettes are used almost exclusively by smokers to quit smoking or reduce the harm from tobacco.
- There is growing evidence for the effectiveness of e-cigarettes as a quitting aid from population studies, longitudinal studies and randomised controlled trials.
The scientific consensus is that e-cigarettes are substantially less harmful than smoking.

- Almost all the harm from smoking is from the tar, carbon monoxide and other toxic chemicals caused by burning tobacco.
- These harmful and potentially harmful chemicals are mostly absent from, or present in substantially lower amounts in, e-cigarette vapour.
- While young people may experiment with e-cigarettes, regular sustained use by never-smokers is very rare and there is very little evidence in support of their role as a gateway product to smoking.

- E-cigarettes have a role in physician practice for smokers who are unable or unwilling to quit smoking with approved therapies.
- There is now sufficient empirical evidence and real-world experience to support their use as a legitimate tobacco harm reduction tool.

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References

Access to a youth-specific service for young adults with type 1 diabetes mellitus is associated with decreased hospital length of stay for diabetic ketoacidosis

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Abstract

Background: Management of type 1 diabetes mellitus in youth with diabetes (YWD) is complex, and glycaemic control often deteriorates during this challenging period. We hypothesise that attendance at a youth-specific diabetes clinic reduces hospital admission rates and length of stay (LOS) for diabetic ketoacidosis (DKA).

Aims: To assess the impact of a youth-specific diabetes service for YWD on DKA admissions in two adjacent local health districts.

Methods: A retrospective cohort analysis of admissions for DKA in YWD aged 15–25 years, presenting to four hospitals in Western Sydney in 2011 was performed. Number of admissions, LOS and DKA severity were assessed. Cost was analysed as a function of LOS. Groups were divided by attendance at a youth-specific diabetes service and no record of attendance.

Results: There were 55 DKA admissions from 39 patients (median age 20.0 years); the majority of admissions (82%) was YWD not supported by a youth-specific diabetes service. Median LOS was significantly longer in the unsupported group (3.0 vs 1.3 days, \( P = 0.028 \)). Median pH at presentation in the unsupported group was significantly lower, 7.11 versus 7.23 (\( P = 0.05 \)). The admission rate was four times greater for those not supported by youth-specific diabetes services, 5.5% compared with 1.6% (\( P = 0.001 \)). The estimated cost saved by youth-specific services was over $250,000 pa.

Conclusions: Lack of access to supported care for YWD during transition from paediatric to adult care has an adverse impact on subsequent DKA admission rates and LOS.
Introduction

Management of type 1 diabetes mellitus (T1DM) in the young adult population is complex and challenging. During this period of transition, the demands of this condition impact not only physical outcomes but psychological development, social life and education as well.\(^1\)

The prevalence of T1DM is increasing every year in Australia, and coordinated specialised services are essential in its management. In 2010, 1.4% of children in NSW were documented as being affected by this chronic condition, and the incidence in Australia remains among the top 10 countries in the world.\(^2\) It was estimated that the number of children aged 0–19 years with T1DM increased by 7% over the period 2006–2016.\(^3\) In NSW, the Western Sydney and South Western Sydney Local Health Districts have projected an increase of more than double that of the rest of the state.\(^5\) The number of young adults aged 15–19 years with diabetes in Western Sydney is expected to have increased by 16% between 2006 and 2016.\(^5\)

Traditionally, children with T1DM are managed in specialist paediatric centres, with regular interactions between healthcare professionals and families in a setting that offers close supervision.\(^6\) As adults, ongoing care of these patients is often assumed by primary healthcare providers, with or without adult endocrinology specialist guidance. This abrupt change between the paediatric and adult healthcare setting, the need for autonomy and the notable differences in healthcare delivery leads to a loss to specialist follow up, with associated deterioration in glycaemic control in young adults with T1DM.\(^4\)–\(^6\) Maintenance of specialist care during this transition period is of significant importance given the unique needs of young adults.\(^5\)\(^,\)\(^7\) Diabetes education in the paediatric setting has usually been directed towards parents or carers, and the understanding of the young person may be assumed. Young adulthood may be associated with multifaceted pressures, including adjustments to home and accommodation status, education and financial hardship.\(^8\)\(^,\)\(^9\)

Poor glycaemic control is common among this population, with lower numbers of young adults achieving glycated haemoglobin (HbA1c) targets than in paediatric settings.\(^2\)\(^,\)\(^10\)\(^,\)\(^11\) Inadequate diabetic control during this period contributes to an increased risk of presentation with diabetic ketoacidosis (DKA), particularly when combined with risk-taking behaviour, such as the use of drugs and alcohol.\(^7\)\(^,\)\(^12\)\(^,\)\(^13\) Suboptimal control is also linked to a high risk of vascular complications in later adulthood and higher relative mortality risks both in the short term, with reports of increased suicide following admission with DKA, and the long term.\(^14\)\(^–\)\(^16\)

Adult services, which specifically tailor healthcare delivery to enable young people to manage safely their chronic disease in the context of normal young adult behaviour, provide valuable age-appropriate support until the young person is able to negotiate adequately adult-orientated services.\(^2\)\(^,\)\(^7\)\(^,\)\(^17\) Previous research has demonstrated that the engagement of young adults with a diabetes clinic dedicated to managing the transition period improved glycaemic control as measured by HbA1c\(^2\)\(^,\)\(^17\) and decreased the number of hospital admissions and the length of stay (LOS) for readmissions with DKA.\(^17\) Furthermore, reduced progression of ketosis to ketoacidosis has been shown to occur in young adults with access to mobile phone support from such clinics.\(^8\)

Although benefits have been documented, there is no proof that the association with a youth-specific diabetes service reduces hospital LOS for young adults with DKA compared with those who do not attend such services. The purpose of this study was to evaluate the impact of a specific age-appropriate service on these parameters. We hypothesised that LOS for DKA may be reduced in young adults who are linked to a youth-specific diabetes service, compared to those who are not, due to greater understanding of management of diabetes. We also hypothesised that the severity of DKA at presentation for young people linked to youth-specific diabetes services should be reduced because of access to specific education on sick day management and provision of after-hours phone support compared with those accessing care in the community as required.

Methods

Subjects

The study population comprised young adults (15–25 years) with a known history of T1DM, who presented with DKA during the period January to December 2011 to four metropolitan tertiary hospitals in two adjacent local health districts (LHDs) in Western Sydney, which serve a referral population of approximately 270 000 youth aged 15–25 years. In Western Sydney, all DKA admissions aged 16 years or over are admitted to the adult hospital rather than the paediatric hospital for the same population. All hospitals within the LHDs were included; these specifically included Westmead Hospital, Nepean Hospital, Auburn Hospital and The Blue Mountains Hospital. No hospitals, apart from a paediatric hospital, within this zoning were excluded from the study.

Study design

A retrospective cohort analysis was performed. Two of the hospitals surveyed offered a youth-specific diabetes service that was available to all patients aged
15–25 years with T1DM within the health service area. The model of care and services offered by the youth-specific diabetes service is summarised in Table 1.

Patients presenting to the emergency department (ED) during the study period who attended either of the youth-specific diabetes clinics were categorised as the ‘supported’ group; the remaining patients presenting to the ED over the study period were categorised as the ‘unsupported’ group.

### Data collection

Electronic medical records and hospital files were reviewed for each presentation. Variables investigated included age, current HbA1c, admission pH, serum bicarbonate, serum ketones measured using the Optium β-ketone test strips with Optium Xceed Meter (Abbott Diabetes Care Inc., Alameda, CA, USA) and length of hospital stay.

Severity of DKA was measured as mild, moderate and severe based on pH and serum bicarbonate collected on admission: pH 7.25–7.30 with bicarbonate 15–18 mmol/L; pH 7.10–7.25 with bicarbonate 10–14 mmol/L and pH <7.10 with bicarbonate <10 mmol/L for mild, moderate and severe respectively. In cases where pH and bicarbonate were discordant, serum bicarbonate was used to classify severity as the results of biochemistry were more reliably available within an hour of ED presentation.

Population health data regarding total numbers of patients aged 15–25 years with T1DM who were living within the referral area of the hospitals from which DKA data were collected were obtained using data from the National Diabetes Services Scheme (NDSS). The NDSS is a government-initiated body that provides support services and information to patients with diabetes, recording age, type of diabetes and address. All patients are registered with the NDSS in order to gain subsidised access to consumables for diabetes care; thus, NDSS records are a reasonable reflection of the numbers of people with diabetes by postcode in Australia.

### Ethics

The study obtained ethics approval as a Quality Assurance project in each of the participating health districts (Western Sydney HREC 2013/5/5.1 (3681) QA; Nepean Blue Mountains LHD QA Study 13/18).

### Statistical analysis

Statistical analysis was performed using the IBM SPSS 18.0 software programme (Armonk, New York, NY, USA). Medians and interquartile ranges were used for descriptive population data. Mann–Whitney U-tests were used to assess differences between the non-parametric variables of the two study arms. Spearman’s rank correlation coefficients were used to analyse the relationship between youth-specific diabetes clinic association and variables of LOS and DKA severity. The Chi-squared test for difference in proportions was used to assess differences in admission rates.

### Results

During the period January to December 2011, there were 55 hospital presentations for DKA from 39 patients aged 15–25 years (median 20 years (18,23)). The number of presentations per patient ranged from one to five, with the majority presenting once (71.4%). Of the 39 patients (55 presentations), 8 (10 presentations) who presented with DKA were supported by a youth-specific diabetes clinic. At the time of the data collection, there were 492 patients known to the youth-specific diabetes services (admission rate 8/492, or 1.6% of the youth-specific diabetes clinic population).

Admissions of supported patients were attributed to pump malfunction (10%), omitted insulin doses (60%), vomiting (20%) and alcohol excess leading to vomiting and dehydration (10%). Patients who were unsupported largely presented for reasons associated with insulin...
omission or infection. Four of the eight supported patients were using insulin pumps. There were no insulin pump patients in the unsupported group. The precipitants for DKA in both the supported and unsupported groups are displayed in Table 2.

The median HbA1c of all presentations was 11.6% (9.7, 13.2) (103 (83, 121) mmol/mol), and the median admission pH was 7.16 (7.05, 7.25) (ref 7.35–7.45). Median serum ketones were 5.1 (4.6, 6.2) mmol/L (ref <0.1), and median serum bicarbonate was 9.0 (5.0, 12.0) mmol/L (ref 22–32). The majority of presentations were categorised as severe DKA (55.5%). The median LOS for the entire cohort was 3.0 (2.4, 5) days.

Demographically, the supported versus unsupported arms were similar in terms of age and HbA1c (Table 3). The majority of presentations of patients who were supported were categorised as mild or moderate DKA (70.0%), whereas presentations from the unsupported group were more likely to have severe DKA (60.0%). The proportion presenting with mild/moderate DKA, compared with severe DKA, in each group was not significant, \( P = 0.08 \); however, the median pH at presentation in the supported group was significantly higher than in the unsupported population (\( P = 0.05 \)). The median LOS was significantly shorter in the supported group at 1.5 days compared to 3.0 days in the unsupported group, \( P = 0.028 \) (Fig. 1). There were no significant differences between the two groups with respect to blood ketones and serum bicarbonate at presentation (Table 3) A weak negative association was noted between LOS and admission pH (\( r = -0.32, P = 0.02 \)), and a weak negative association was noted between LOS and admission serum bicarbonate (\( r = -0.32, P = 0.02 \)).

At the time of the study period, there were 1052 patients aged 15–25 years with T1DM living in the area serviced by the four hospitals (NDSS). During this time period, 492 were linked to a youth-specific diabetes clinic, leaving an estimated 560 patients receiving non-specialised care within the community setting only. There was a significant difference in proportions admitted from each group, 1.6 versus 5.5% (\( P = 0.001 \)) in supported and unsupported groups respectively.

The average cost per day for a hospital bed for DKA was estimated to be $2087 at the time of the study. This cost was derived based on figures obtained from the New South Wales Department of Health. Based on a difference in median LOS of 1.5 versus 3.0 days in supported versus unsupported arms and a total number of admissions in 2011 of 10 versus 45, respectively, the estimated cost saved by the transition service using reduction in bed days alone was $250 500 (Table 4). In addition to basic costs for a hospital clinic, the salary for a clinical nurse consultant dedicated to a specific transition clinic was approximately $120 000 per annum at the time of the study. Overall, accounting for inclusion of this salary, the estimated hospital saving was therefore $130 500, thus supporting the economic benefit and implementation of transition services.

**Discussion**

This study aimed to assess whether support from a youth-specific diabetes service reduced hospital LOS as compared with accessing support as needed in the community. We found a statistically significant (\( P < 0.05 \)) shorter LOS of 1.5 days in patients who were supported

---

Table 2 Precipitants for DKA in supported versus unsupported subjects

<table>
<thead>
<tr>
<th>DKA precipitant</th>
<th>Supported ( n (%) )</th>
<th>Unsupported ( n (%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting illness</td>
<td>2 (20)</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>Omitted/insufficient insulin</td>
<td>6 (60)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Infection</td>
<td>0 (0)</td>
<td>14 (31.1)</td>
</tr>
<tr>
<td>Alcohol/drug use</td>
<td>1 (10)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Insulin pump failure</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unclear precipitant</td>
<td>0 (0)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>Total</td>
<td>10 (100)</td>
<td>45 (100)</td>
</tr>
</tbody>
</table>

DKA, diabetic ketoacidosis.

**Table 3 Clinical and biochemical characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supported median (LQ, UQ)</th>
<th>Unsupported median (LQ, UQ)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19.0 (17.0, 20.5)</td>
<td>20.0 (18,23)</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (ref &lt;6.5%, &lt;=8 mmol/mol)</td>
<td>11.9 (9.8, 12.8)</td>
<td>11.6 (9.9, 13.2)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>[107 (84, 116)]</td>
<td>[103 (85, 121)]</td>
<td>NS</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>1.5 (1.0, 2.0)</td>
<td>3.0 (2.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Admission pH (ref 7.35–7.45)</td>
<td>7.23 (7.17, 7.25)</td>
<td>7.11 (7.03, 7.22)</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum ketones (ref &lt;0.5 mmol/L)</td>
<td>4.8 (4.4, 5.2)</td>
<td>5.4 (4.6, 6.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum bicarbonate (ref 23–28 mmol/L)</td>
<td>10.0 (8.1, 11)</td>
<td>8.0 (4.12)</td>
<td>NS</td>
</tr>
</tbody>
</table>

LQ, lower quartile; NS, not statistically significant; UQ, upper quartile.
by a youth-specific diabetes clinic. Additionally, we found a significant difference in pH at admission, potentially reflecting milder DKA at presentation in those youth with diabetes (YWD) supported by a youth-specific diabetes service.

Table 4 Cost analysis based on support by the youth-specific diabetes service

<table>
<thead>
<tr>
<th></th>
<th>Supported</th>
<th>Unsupported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admissions (n)</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>Median length of stay (days)</td>
<td>1.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Cost per day</td>
<td>$2087</td>
<td>$2087</td>
</tr>
<tr>
<td>Cost per length of stay</td>
<td>$3130</td>
<td>$6261</td>
</tr>
<tr>
<td>Total cost per year</td>
<td>$31 300</td>
<td>$281 800</td>
</tr>
</tbody>
</table>

YWD admitted with DKA have poor control, as evidenced by HbA1c >11% (97 mmol/mol). This finding supports previous research that has suggested that DKA presentations in this age group are associated with worse glycaemic control.\textsuperscript{7,10} The lack of difference in HbA1c between the two groups suggests that YWD who have HbA1c >11% (97 mmol/mol) are more likely to present with DKA consistent with previous publications. However, despite the similarities in poor control in all YWD admitted to hospital with DKA, those who were supported by youth-specific diabetes services had a better outcome with less severe DKA at presentation and shorter LOS. Based on proportions of young people admitted from supported and unsupported groups, with
a fourfold greater admission rate in unsupported YWD, one would surmise that a greater proportion of unsupported YWD would have poor control. By comparison, the average HbA1c for patients supported by the youth-specific diabetes clinics described was 8.6% (70 mmol/mol), much lower than those admitted to hospital and lower than that reported in the literature for this age group, with many studies reporting HbA1c between 9 and 10% (75–86 mmol/mol).  

The difference in admission pH at the time of presentation may be due to earlier presentation of patients supported by a youth-specific diabetes service or may reflect the introduction of appropriate treatment at home prior to presentation. We did not have access to data to indicate whether those patients who were supported by the clinic had utilised the phone support service at either centre prior to presentation to hospital in 2011 or had some existing knowledge about management of sick days. Age-appropriate education regarding sick day management and hyperglycaemia is provided regularly during clinic attendance, and patients are encouraged to telephone if unwell.

**Care of unsupported patients**

The reduced number of presentations from patients linked to a youth-specific diabetes service is encouraging. There is concern, however, surrounding the estimates of patients not receiving support from a youth-specific specialist clinic. We can only speculate with respect to their behaviours and access to healthcare services. They may be receiving care from endocrinologists in private practice, although this is speculated to be less likely given the socioeconomic demographics of the population surveyed. Even if accessing care outside of hospital clinics, there is arguably less access to after-hours phone support and diabetes education in this setting. General practice (GP) care may be utilised, although previous data have documented that only 18% of all patients with diabetes (type I and II) complete a cycle of care, including complications screening in the GP setting. Furthermore, access to nurse educators with expertise in diabetes care is more limited in GP. It is possible that a significant proportion of this group is lost to follow up, only seeking medical advice as needed or to obtain prescriptions for insulin. Previous research examining children and adolescents accessing specialist diabetes services has found that the proportions of patients aged 15–17 years who seek care were significantly lower than those captured in the under 15 years age group. This emphasises a need to determine what factors prevent YWD from accessing specialist care for diabetes and to characterise the patterns of their healthcare utilisation when not attending specialist care.

**Reasons for loss to follow up**

Loss to follow up after review by a youth-specific diabetes service is rare given the ongoing recall and reminder systems in place. The loss to follow up rate in 2011 for the youth-specific clinics described was 5%, considerably lower than documented rates in the literature. Elsewhere in Australia, data showed that 35% of patients who transitioned from paediatric services were lost to follow up by diabetes specialist services. In the paediatric setting, with close involvement of parents, the model of care may direct education at parents. If patients leave paediatric care before transition occurs, it is possible that they have limited understanding of the importance of regular review, less understanding of their diabetes management and a greater potential to develop both short- and long-term complications. Lifestyle changes may contribute to these complications, including change in accommodation and financial status and less oversight and advice regarding diabetes management from parents and carers. Varying motivations for self-care coupled with potential engagement in high-risk behaviour, such as alcohol and drug use, can lead to an increase in admissions with DKA.

Loss to follow up is of concern during the transition given the vulnerability of patients and the potential impact on long-term health behaviours. Lack of age-specific education and neglect of diabetes complications screening may negatively impact disease progression and control. There are some limitations noted with this study. Firstly, the small admission sample size is recognised. Secondly, the number of patients aged 15–25 years with T1DM in the health service area is based on NDSS data; hence, exact figures may be inaccurate due to young people frequently changing address, which may not be updated with the registry. Lastly, we can only hypothesise behaviours of the unsupported group as we have no data on the routine care they are receiving or from whom. However, the population is from a more socially disadvantaged area of Sydney, and unless supported by family, young people are unlikely to access private endocrinologist care and are more likely to rely on general practitioners for management. Conversely, it is possible that patients who are supported by a youth-specific service may be more diabetes-conscious, engaged with their primary care physician and have better social support networks. These data were not collected or confirmed specifically in our study, although it is recognised that such factors may be confounders with respect to DKA presentation rates.

Future research should aim to characterise the behaviour of these supposedly unsupported young adults to meet the needs of this group by linking them...
to appropriate age-specific diabetes services. Furthermore, the proof of economic benefit provides encouraging evidence, suggesting the need for wider introduction of youth-specific diabetes services. Potential models of specialist care, separate from hospitals, require exploration to increase service accessibility for YWD. The current data highlight the need for new ways to access and support those patients who are not currently managed by youth-specific diabetes services as existing models of care reach only around 50% of young people with T1DM. Lastly, given that there was only a small number of patients using insulin pumps, the influence of pump use on DKA admission risk could not be evaluated. This area warrants further investigation in future studies.

**Conclusion**

Lack of supported care in T1DM for YWD has a significant negative impact on DKA admission rates and LOS. Transition-specific services for YWD significantly reduced costs associated with hospital admission and positively influenced the availability of resources in an increasingly burdened healthcare system. New strategies to improve access for all YWD to age-appropriate services are needed.

**Acknowledgements**

The study investigators acknowledge the additional support staff, including endocrinologists and nurses who help with the running of the YWD service at the hospitals described.

**References**


7. Peters A, Laffel L, Group ADATW. Diabetes care for emerging adults: recommendations for transition from pediatric to adult diabetes care systems: a position statement of the American Academy of Pediatrics, the American Association of Clinical Endocrinologists, the American Osteopathic Association, the Centers for Disease Control and Prevention, children with diabetes, the Endocrine Society, the International Society for Pediatric and Adolescent Diabetes, Juvenile Diabetes Research Foundation International, the National Diabetes Education Program, and the Pediatric Endocrine Society [Erratum appears in Diabetes Care 2012; 35: 191]. **Diabetes Care** 2011; **34**: 2477–85.


Thirty-day mortality after systemic anticancer treatment as a real-world, quality-of-care indicator: the Northland experience

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Key words
30-day mortality, systemic anticancer treatment, real world quality of care indicator, Whangarei Base Hospital, Northland, New Zealand, auditing medical oncology practice.

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Abstract

Background: Systemic anticancer treatment (SACT) at the end of life is considered poor practice due to its futility and associated toxicities. Consequently, 30-day mortality after SACT is increasingly recognised as a potential real-world quality-of-care indicator in medical oncology.

Aims: Whangarei Base Hospital (WBH) provides outpatient SACT treatment to all patients living in the Northland region of New Zealand. The goal of this study was to report our 30-day mortality after SACT and to contribute to the experience of its use in Australasia.

Methods: In this retrospective study, the WBH electronic database was searched to identify all patients who had received SACT in WBH from 1 January 2012 to 31 December 2016. Patients who died within 30 days of their last treatment were short-listed. Records were reviewed identifying key demographic, disease, treatment and mortality data. Composite 30-day mortality index and that of each tumour stream were calculated. Key findings were described using descriptive statistics.

Results: Over 5 years, 1103 patients received SACT in WBH, with 57 patients dying within 30 days of treatment, resulting in a composite 30-day mortality rate of 5.17%. One patient died receiving curative intent SACT. More deaths occurred in SACT-naïve patients and during the first two cycles of therapy. Of the deaths, 28% was attributed to SACT, while 59.7% was attributed to cancer progression.

Conclusion: Thirty-day mortality rates were comparable to studies from larger institutions. We demonstrated the feasibility of this index for auditing practice in smaller oncology units over a longer timeframe.

Introduction

Systemic anticancer treatment (SACT) encompasses a heterogeneous array of treatment agents, ranging from conventional chemotherapy to drugs that target cancer or the immune system at a molecular level. As one of the pillars of modern cancer treatment with a solid evidence base, the use of SACT for the cure and palliation of cancer is well documented.

However, like most medical interventions, SACTs have an inherent potential of causing harm to patients. It is increasingly recognised that the administration of SACT during the last month of life constitutes poor practice based on the notion of medical futility or, in some cases, the direct toxic consequence of therapy.¹⁻³ In 2012, the American Society of Clinical Oncology (ASCO) highlighted the need to address the problem of prescribing chemotherapy at the end of life as one of the top five practice-changing priorities.⁴

There is paucity of data on patient outcomes and treatment toxicity rates after SACT outside of clinical trials, where strict parameters curtail generalisability in real-life practice.⁵ The need for a real-world benchmark has generated interest in 30-day mortality after SACT as a viable indicator to measure and audit for quality improvement purposes.⁶ This metric is not a new concept in cancer management as it has been widely used within the practice of surgical oncology for many years.⁷,⁸ However, within medical oncology circles, this has only started to gain momentum as a potential benchmark.

Studies in Japan, UK, Australia and the United States have been published in the last decade.⁹⁻¹¹ These studies were performed in large oncological institutions and demonstrated feasibility. The benchmark has been particularly accepted as a performance indicator in the United Kingdom, where in 2011, the national cancer strategy for England proposed 30-day mortality as a national clinical indicator of avoidable harm in
This subsequently led to the publication of the first national study on 30-day mortality focused on breast and non-small-cell lung cancer in 2014, followed by a trust-level companion report.11,12 Besides revealing disparity amongst National Health Service (NHS) hospital trusts, the study also examined patient-, tumour- and treatment-related factors and their association with the risk of this outcome.

Apart from a single-institution study published by Salih et al., no other 30-day mortality post-SACT data from New Zealand was found at the time of our literature search.13 Currently, key performance indexes (KPI) for medical oncology services nationwide are focused on service provision, which includes timely access to appointments, diagnostic testing and treatment for patients, in tandem with the Ministry of Health (MOH) ‘Faster Cancer Treatment’ programme.14 The MOH is presently exploring multiple clinical indicators that could be used to audit quality of care.

This retrospective study was conducted to document our 30-day mortality rate after SACT while exploring its utility as a tool for auditing clinical practice and improving quality of care in an outpatient oncology treatment unit. In addition, we hope to contribute to the growth and experience in the use of this indicator.

Methods

Whangarei Base Hospital (WBH) is a secondary referral hospital servicing a population of 170 000 in the Northland region of New Zealand. The hospital provides outpatient medical oncology and malignant haematology services. Patients requiring inpatient SACT or concurrent chemoradiotherapy are referred to Auckland City Hospital. Patients who develop complications from SACT and require hospitalisation are admitted under the general medical team in WBH, with input from the oncology team.

We defined SACT as all chemotherapy, targeted biological therapy (e.g. tyrosine kinase inhibitors, monoclonal antibodies) and immunotherapy, with the purpose of treating both solid organ and haematological malignancies, regardless of the route of administration. We excluded endocrine and other supportive treatment agents, such as bisphosphonates, to facilitate data comparison with contemporary studies and due to the limited life-threatening toxicity of these treatments.

All SACT treatment activities in our unit are captured in WBH’s electronic database by means of MOH-defined purchased unit codes (PUC) logged against a unique patient identifier (national health index). After ethics approval, the electronic database was queried to identify all patients who had received SACT over a period of 5 years starting from 1 January 2012 to 31 December 2016. The selected list was reviewed to ensure fidelity. The tumour stream of each patient was determined, with patient electronic records reviewed where there were discrepancies.

These results were interrogated electronically to identify a list of patients who had died within 30 days of their last administered dose of SACT. The electronic and hardcopy notes of each patient in the list were then analysed by the study team (registrar/consultant oncologist). Data on patient demographics (age, gender, ethnicity, body mass index (BMI), Eastern Cooperative Oncology group (ECOG) functional status, comorbidities), disease characteristics (tumour stream, stage where applicable), treatment received (type of SACT, treatment line and cycle, treatment intent) and mortality (year, number of days from last dose, location of death) were collected. Cause of each death was identified from hospital records and death certificates. Where possible, the cause of death was determined by the audit team as treatment related (in all cases of sepsis and where treatment toxicity was felt to contribute significantly to mortality), disease related (cancer progression/complications) or an unrelated medical event.

The composite 30-day mortality rate and the rate across each major tumour stream over a duration of 5 years were calculated. For breast cancer and non-small-cell lung cancer (NSCLC), we calculated the 30-day mortality over 5 years for both adjuvant and palliative cases for comparison with published data. Key demographic, disease, treatment and mortality features were also analysed using descriptive statistics.

Results

Within the designated 5-year period, 1125 unique patients were identified from the WBH electronic database as having received SACT. The actual number was confirmed at 1103, with 22 patients excluded as they had received treatment for non-malignant conditions (e.g. patients with idiopathic thrombocytopenic purpura receiving rituximab). On electronic data interrogation, 60 of the total patients were identified as having died within 30 days of their last dose of SACT. When patient records were physically reviewed, 3 deaths were found to be outside the 30-day period, bringing the actual number that met our study definition to 57.

Table 1 summarises the key findings from this study. The composite 30-day mortality after SACT rate across all tumour streams in our unit was 5.2%. The median age was 68 years, with the youngest aged 21 years and the oldest aged 81 years. More women received SACT therapy overall (56.6%), but more men died within 30 days of SACT as compared to women (60% in men...
compared to 40% in women). Of 57 patients who died within 30 days of SACT, 15 were Maori (26%), closely matching the proportion of Maori patients who received SACT over the 5-year period (24%).

Of 45 patients in whom we could calculate the BMI at the time of their last treatment, only 2 patients were underweight, as opposed to 7 who were classified obese. In 14 cases, the ECOG performance status score could not be determined from the notes. Of the eight (14%) who had ECOG scores above two, seven received conventional chemotherapy while one received immunotherapy.

Of the 1103 patients, 82% received treatment for solid organ malignancies, while 18% received treatment for haematological malignancies. The 30-day mortality cases mirrored this, with 49 patients (86%) treated for solid organ tumours, and the remaining 8 patients (14%) treated for haematological malignancies. Table 2 summarises the 30-day mortality rates based on tumour streams. Of the 57 patients who died within 30 days of SACT, 13 (22.8%) were receiving treatment for metastatic colorectal cancer, representing the largest group in our data. Ten patients with lung cancer died within 30 days of treatment, with equal numbers of NSCLC and small-cell lung cancer patients (SCLC).

Only 1 of the 57 patients died while receiving curative-intent SACT for diffuse large b cell lymphoma. The 30-day mortality rates in breast cancer and NSCLC treated with palliative intent was 3.8% and 7.1% respectively. Notably, three out of four patients receiving SACT for amyloidosis died within the 30-day time frame. Other tumour streams that documented relatively high 30-day mortality rates include high-grade neuroendocrine tumours (66.7%), malignant melanoma (25%) and upper gastrointestinal malignancies (9.4%), although the total number of patients receiving treatment for these malignancies was low. Of note, an increase in the number of patients receiving SACT for malignant melanoma was documented in 2016, consequent to New Zealand Pharmaceutical Management Agency’s (Pharmac) decision to fund nivolumab and pembrolizumab.

Table 1 Key study findings and treatment regiments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly 5-fluorouracil, folic acid</td>
<td>5</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1</td>
</tr>
<tr>
<td>Bortezomib, rituximab, dexamethasone (BDR)</td>
<td>1</td>
</tr>
<tr>
<td>Capcitabine</td>
<td>2</td>
</tr>
<tr>
<td>Capcitabine, oxaliplatin (CAPOX)</td>
<td>5</td>
</tr>
<tr>
<td>Epirubicin, cisplatin, capcitabine (ECX)</td>
<td>1</td>
</tr>
<tr>
<td>Carboplatin, etoposide</td>
<td>6</td>
</tr>
<tr>
<td>Carboplatin, gemcitabine</td>
<td>2</td>
</tr>
<tr>
<td>Carboplatin, paclitaxel</td>
<td>2</td>
</tr>
<tr>
<td>Cisplatin, 5-fluorouracil, folic acid</td>
<td>1</td>
</tr>
<tr>
<td>Low-dose cytarabine</td>
<td>1</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>1</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>5</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>5</td>
</tr>
<tr>
<td>Cisplatin, gemcitabine</td>
<td>1</td>
</tr>
<tr>
<td>Docetaxel, herceptin</td>
<td>1</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>2</td>
</tr>
<tr>
<td>5-Fluorouracil, irinotecan, folic acid (FOLFIRI)</td>
<td>1</td>
</tr>
<tr>
<td>Melphalan</td>
<td>1</td>
</tr>
<tr>
<td>Bortezomib, melphalan, prednisone (VMP)</td>
<td>1</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>1</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>3</td>
</tr>
<tr>
<td>5-Fluorouracil, folic acid, oxaliplatin (FOLFOX)</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab, cyclophosphamide, dexamethasone (RCD)</td>
<td>1</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>3</td>
</tr>
</tbody>
</table>

SACT, systemic anticancer treatment; WBH, Whangarei Base Hospital.

Table 2 30-Day mortality according to tumour stream

<table>
<thead>
<tr>
<th>Tumour stream</th>
<th>Total patients</th>
<th>30-Day mortality numbers</th>
<th>30-Day mortality index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All breast cancer</td>
<td>245</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Breast curative</td>
<td>167</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Breast palliative</td>
<td>78</td>
<td>3</td>
<td>3.8</td>
</tr>
<tr>
<td>All lung cancer</td>
<td>159</td>
<td>10</td>
<td>6.3</td>
</tr>
<tr>
<td>NSCLC adjuvant</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NSCLC palliative</td>
<td>70</td>
<td>5</td>
<td>7.1</td>
</tr>
<tr>
<td>SCLC</td>
<td>68</td>
<td>5</td>
<td>7.3</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lower GI</td>
<td>200</td>
<td>13</td>
<td>6.5</td>
</tr>
<tr>
<td>Upper GI</td>
<td>107</td>
<td>10</td>
<td>9.3</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>16</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>72</td>
<td>3</td>
<td>4.17</td>
</tr>
<tr>
<td>Urogenital</td>
<td>67</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Head and neck</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NET</td>
<td>3</td>
<td>2</td>
<td>66.6</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myeloma</td>
<td>65</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>4</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>101</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CLL</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MDS/leukaemia</td>
<td>13</td>
<td>1</td>
<td>7.7</td>
</tr>
</tbody>
</table>

CNS, central nervous system; CLL, chronic lymphocytic lymphoma; GI, gastrointestinal; MDS, myelodysplasia; NET, neuroendocrine tumour; SCLC, small-cell lung cancer patient; NSCLC, non-small-cell lung cancer.
pembrolizumab. Three out of four patients with malignant melanoma who died within 30 days of their last treatment were receiving immunotherapy.

Forty three (75.4%) of the 30-day mortality deaths occurred during first line treatment, while four patients (7%) were identified to have died while on third-line therapy. The remainder died on second-line therapy. Thirty-eight deaths occurred during the first two cycles of SACT, with two deaths occurring at the eight cycle. A majority (86%) were receiving cytotoxic chemotherapy, while the remaining patients were evenly distributed between immunotherapy and combination chemotherapy/monoclonal antibody therapy.

Analysis of patient mortality data showed an equal distribution of deaths over the 30-day period, with 56% of patients dying within the first 2 weeks. Table 3 summarises the cause of deaths. Thirty five (61.4%) patients died of disease-related causes (31 of disease progression, 4 of cancer complication), while 15 (26.8%) deaths were treatment related. Sepsis was the most common treatment-related complication leading to death. Of this group, 6 out of 11 patients had documented neutropenia. Other causes of treatment-associated deaths included acute renal failure (2), decompensated heart failure (1) and fulminant hepatitis B (1). The overall treatment-related death rate within 30 days of SACT over the 5-year duration was 1.35%. Sixteen (28%) patients died in hospital, while the rest died in hospice or at home.

Discussion

Our audit demonstrated the feasibility of 30-day mortality as an indicator for accessing quality in real-life practice in a regional outpatient oncology unit in New Zealand. This study is unique as it audited 30-day mortality over 5 years, as opposed to other contemporary studies, which chose shorter time frames (6–18 months).3,6,12,13

We extracted substantial demographic, disease, treatment and mortality data from the 57 patients who died within 30 days after SACT. We believe the collected data would facilitate the identification of pivotal factors in our treatment population that have been associated with higher 30-day mortality rates in larger studies.

Our overall 30-day mortality rate was comparable to several large oncology treatment centres abroad and in New Zealand (Royal Marsden Hospital, London: 7.5%;10 Belfast City Hospital, UK: 4.5%;13 Gold Coast Hospital, Australia: 6.9%).1 A recent study from two large academic centres in the United States with regards to 30-day mortality rates according to tumour streams documented higher 30-day mortality rates across numerous tumour streams (colorectal: 12%; breast: 9%).6 Within Australasia, the most comparable study to ours in terms of population and institutional size reported a 30-day mortality rate of 3.4%, although this study was smaller in comparison.5

Our 30-day mortality rates for both adjuvant and palliative SACT in NSCLC and breast cancer was more favourable when compared to those reported by Wallington et al, although this should be viewed cautiously in the light of the difference in study size.12 Our treatment-related deaths (26.8%) were higher than those reported in other centres (e.g. Southern Blood and Cancer Services, New Zealand: 18.6%;13 Gold Coast Hospital: 11.2%).1 This disparity may be caused by the lack of standardisation in the definition of 30-day mortality (30 days after the first day of the last cycle of SACT or 30 days after the last dose of SACT) and what should be classified as treatment-related deaths. We deliberately placed a low threshold of labelling deaths as treatment associated. Nevertheless, these cases are currently being reviewed.

There are several limitations to this audit, with data quality being the most important. This is not unique to this study as this has been widely reported.10,12 There is a possibility that a proportion of patients on oral treatment agents only (e.g. tyrosine kinase inhibitors, capecitabine, temozolamide) may have been missed in our dataset. In addition, inaccuracies within the electronic database necessitated a labour-intensive review of the data to minimise errors. Lastly, among the 57 patients who died within 30 days of SACT, there were missing documentation of ECOG functional status (24.6%), BMI (21%) and cause of death (10%). This has highlighted the need to implement better clinical record and data collection practices.

We did not look at the association between clinician factors and 30-day mortality after SACT in this study. Giorgi et al. reported that a high proportion of patients who received treatment during their last month of life did so because of the recommendation of their oncologist, with only a small number requesting chemotherapy.

Table 3 Cause of death in the 57 patients who died within 30 days of last systemic anticancer treatment

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Subcategory</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease/cancer related</td>
<td>Disease progression</td>
<td>31 (54.4%)</td>
</tr>
<tr>
<td></td>
<td>Cancer-related complications</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Treatment associated</td>
<td>Sepsis</td>
<td>11 (19%)</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>2 (3.5%)</td>
</tr>
<tr>
<td></td>
<td>Fulminant hep B</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Other causes</td>
<td></td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Not defined</td>
<td></td>
<td>6 (10.5%)</td>
</tr>
</tbody>
</table>
despite being advised against it.\textsuperscript{16} Bluhm et al. described the paradox of oncologists prescribing late chemotherapy, highlighting several clinician factors (e.g. difficulty communicating cessation of treatment, feeling of responsibility, prognostic uncertainties) as major contributors to this practice.\textsuperscript{17}

Encouragingly, 12 of the 57 patients in our study had their chemotherapy stopped by their oncologist due to disease progression or decline in performance status when pre-assessed for the next cycle. In two out of three cases where clear disease progression was documented, patients’ insistence to continue with therapy was documented. It may be interesting to examine clinician factors in future studies.

There remain formidable challenges to the use of 30-day mortality for clinical governance benchmarking. The concept is somewhat simplistic as a more conservative approach to treatment will lower the 30-day mortality rate, but such an approach may not necessarily be beneficial to patients as declining treatment for some patients may prevent them from receiving valuable survival and palliation benefits.\textsuperscript{1} In addition, the acceptable risk of treatment that a patient would be willing to accept is likely to be variable between individuals. Regional, national and international differences in the provision of cancer care and the limited data outside of the UK will make benchmarking difficult.

In our experience, the composite 30-day mortality rate is a more feasible index for smaller oncology treatment centres. The validity of our 30-day mortality rates in smaller tumour streams is questionable due to limited numbers despite the significantly longer study duration. However, reviewing 30-day mortality in each tumour stream has been helpful in triggering discussions about practice change. For instance, we are currently reviewing the safety of administering outpatient SACT for the treatment of amyloidosis in our unit given the findings.

SACTs are also becoming increasingly heterogeneous with varying tolerability and side-effects. While the use of conventional chemotherapy is discouraged in patients with poorer performance status, there is ambiguity as to whether the same caution should be accorded to other less-toxic therapies. For instance, in our study, we recorded a high 30-day mortality rate amongst malignant melanoma patients receiving treatment. Three out of four of these patients were receiving immunotherapy, with one recording an ECOG performance status of 3.

**Conclusion**

Thirty-day mortality after SACT has the potential to provide a viable real-world clinical indicator that can be used to steer clinical quality initiatives in medical oncology and improve cancer patient care. While it was reassuring to note that our results were comparable to published data from larger oncology centres, the experience of conducting this audit has helped us identify key areas requiring practice review. Finally, we hope our data would contribute to the growing national and international interest and utility of this indicator.

**Acknowledgement**

We acknowledge the help we received from our colleagues in Whangarei Base Hospital, who assisted us in data extraction. Also special thanks to Dr Abbey Jebbs for helping us edit this report.

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Full blood count as an ancillary test to support the diagnosis of giant cell arteritis

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Key words
giant, cell, temporal, arteritis, blood, count.

Abstract

Background: Temporal artery biopsy is considered the investigation of choice to diagnose definitively giant cell arteritis (GCA) in patients with compatible symptoms. However it is invasive and not completely sensitive. Serum markers, particularly erythrocyte sedimentation rate (ESR), can be supportive, but are not definitive in individual cases.

Aims: To investigate whether indices derived from the full blood count, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were associated with a positive biopsy in patients with suspected GCA.

Methods: The clinical and pathological details of 537 patients undergoing temporal artery biopsy at our institution from 1992 to 2015 were reviewed.

Results: In univariate analysis high platelets (odds ratio (OR) 4.44, \( P < 0.001 \)), NLR (OR 1.81, \( P = 0.02 \)), PLR (OR 3.25, \( P < 0.001 \)), C-reactive protein (CRP) (OR 3.00, \( P < 0.001 \)), ESR (OR 3.62, \( P < 0.001 \)) and increased age (OR 1.03, \( P = 0.006 \)) were strongly associated with a positive biopsy. In multivariate modelling only high platelets (\( P < 0.001 \)) and ESR (\( P = 0.049 \)) maintained significance.

Conclusions: We conclude that the presence of thrombocytosis and high NLR, PLR, ESR and CRP can all be used clinically to support the diagnosis of GCA prior to biopsy. Of particular note, in multivariate modelling the presence of thrombocytosis is a stronger predictor of a positive temporal artery biopsy than ESR. Therefore, careful consideration of the findings in a full blood count can be used to predict the likelihood of a positive temporal artery biopsy in patients with suspected GCA.

*These authors contributed equally to this study.

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Conflict of interest: None.
Introduction

Giant cell arteritis (GCA) is a systemic vasculitis of unknown aetiology with a predilection for the large and medium arteries of the head and neck.\(^1\) GCA is the most common systemic vasculitis in the adult population.\(^2\) If treatment is not initiated promptly, GCA can lead to severe and irreversible ischaemia of areas supplied by affected vessels, in particular the ophthalmic artery, ultimately resulting in ipsilateral blindness.\(^3\)

The determination of serum inflammatory biomarkers, most commonly erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), has established roles in the assessment of patients with suspected GCA. However, these markers are neither sensitive nor specific in individual patients and there is some debate concerning their utility in routine clinical practice.\(^4,5\)

The white blood cell count (WBC) and the relative ratios of different white cells are classic indicators of inflammation. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) have recently been extensively investigated as markers of overall survival in malignancies, cardiovascular conditions and other diseases.\(^6-9\) Whilst an association between thrombocytosis and GCA has previously been reported,\(^10,11\) there is no literature to date examining the relationship between GCA and the NLR, PLR and MLR. This is surprising given early evidence of the diagnostic role of the NLR in other vasculitic conditions, such as Behcet disease, Kawasaki disease and Henoch–Schonlein purpura.\(^12-14\) To address this gap in knowledge and to inform clinical practice better, we sought to assess the role of the full blood count and derived variables, including NLR, PLR and MLR, in predicting a definitive diagnosis of GCA.

Methods

The computerised database of the department of anatomical pathology, Royal North Shore Hospital, was searched for all temporal artery biopsies received for pathological examination from 1 January 1992 to 31 December 2015. During this period the department performed centralised surgical pathological testing for four community hospitals and one quaternary referral centre.

The pathology report of all cases was reviewed and each case was classified as either positive for vasculitis or negative for vasculitis. Standard histopathological criteria were used during this time period to define the presence of a positive biopsy based on the American College of Rheumatology guidelines,\(^15\) requiring the identification of a vasculitis characterised by a predominance of mononuclear cells or granulomatous inflammation. If the biopsy report was ambiguous, the original slides were reviewed by an experienced surgical pathologist (AG) blinded to other parameters to assign the biopsy into either positive or negative categories. The full blood count, ESR and CRP results determined on blood drawn prior to biopsy were recorded. Patient age and gender as well as biopsy site were also noted.

We considered all biopsy positive patients as being positive for GCA and all biopsy negative patients as being negative for GCA. The NLR was defined as neutrophils ($\times10^9$/L) divided by lymphocytes ($\times10^9$/L), MLR defined as monocytes ($\times10^9$/L) divided by lymphocytes ($\times10^9$/L) and PLR defined as platelets ($\times10^9$/L) divided by lymphocytes ($\times10^9$/L).

All statistical analysis was conducted by Statistical Analysis Software v9.4 (SAS Institute, Cary, NC, USA). The cohort was analysed using descriptive statistics of patient characteristics and multiple regression of explanatory variables. The study was approved by the Northern Sydney Local Health District Ethics Committee who provided an approval number: RESP/14/91 and the authors confirm that the research was conducted in compliance with the Helsinki Agreement.

Results

Patient demographics

A total of 537 patients underwent temporal artery biopsy between January 1992 and December 2015. Of these, 126 (23.5%) were found to have a positive result. The clinical, serological and full blood count characteristics are presented in Table 1. Briefly, the mean age at diagnosis was 75.9 year (range 55–90) in patients with a positive biopsy and 73.1 (range 16–94) in those with a negative biopsy ($P = 0.006$). More females underwent temporal artery biopsy, however the proportions of female and patients with positive and negative biopsies were similar (67.9% vs 69.1%, $P = 0.860$).

Erythrocyte sedimentation rate

Of the 537 total patients, 373 patients were tested for the ESR prior to surgery. We considered an ESR result of ≤50 mm/h as a negative result and a result of >50 mm/h as a positive result, based on previous studies and local therapeutic guidelines.\(^16\) Of 84 patients who had GCA, 59 (70.2%) also had an elevated ESR, compared to only 107 (37.0%) of the 289 patients without GCA (odds ratio (OR) 4.17, $P < 0.0001$, 95% confidence interval...
CI 2.45–7.10). Receiver operating characteristic (ROC) curve analysis demonstrated an area under the curve (AUC) of 0.67 (Fig. 1).

**C-reactive protein**

A total of 373 patients in the cohort was also tested for the CRP. We considered a CRP of $\geq 24.5$ mg/L as a positive result based on previous studies and local therapeutic guidelines. Based on this cut-off, 69.6% of patients who had GCA also had an elevated CRP, compared to only 43.5% who did not have GCA (OR 3.04, $P < 0.0001$, 95% CI 1.77–5.14). ROC analysis demonstrated an AUC of 0.63.

**Thrombocytosis**

A total of 399 patients had platelet count recorded in our study. We defined an elevated platelet count to be $>400 \times 10^9$/L, which is two standard deviations from the population average and therefore used as the upper limit of the reference range in our laboratory. We found 49.4% of those with GCA had an elevated platelet count compared to 18.4% in those without GCA (OR 4.36, $P < 0.0001$, 95% CI 2.61–7.30). ROC analysis demonstrated an AUC of 0.66 (Fig. 2).

**Neutrophil-to-lymphocyte ratio**

We were able to identify a NLR on preoperative blood in 414 patients in our cohort. As there is no previous

![ROC Curve for Erythrocyte Sedimentation Rate](image_url)

**Figure 1** Receiver operating characteristic (ROC) curve demonstrating the relationship between raised ESR and a positive temporal artery biopsy. The area under the curve (AUC) is 0.67.
information on NLR in GCA, we considered an elevated NLR to be those in the upper quartile of the cohort, of which the threshold was found to be $9.35 \times 10^9/L$. Of the 90 patients who had GCA, 34.4% (31) had an elevated NLR, compared to only 22.5% (73) of the other 324 patients in the control group. We found this difference to be statistically significant (OR 1.85, $P = 0.019$, 95% CI 1.11–3.10) on univariate regression analysis. ROC analysis demonstrated an AUC of 0.55 (Fig. 3).

As a result, positive likelihood ratio (LR+) was found to be 1.53 and negative likelihood ratio (LR−) was 0.85.

**Monocyte-to-lymphocyte ratio**

We recorded 399 patients with a Monocyte-to-Lymphocyte ratio in our cohort. Whilst there appeared to be an association between MLR and GCA, we were unable to find a level (ROC AUC = 0.54) demonstrating statistical significance.

**Platelet-to-lymphocyte ratio**

A total of 399 out of the 537 patients in our cohort had a PLR recorded. As there is no prior literature examining the relationship between PLR and GCA, we again considered an elevated result to be those in the upper quartile of the cohort, corresponding to a threshold of 370. At this level, we found that 43.8% (39) of the 89 patients with GCA had an elevated PLR compared to 19.4% (60) of the 310 patients without GCA. We found that this result was extremely statistically significant (OR 3.34, $P < 0.0001$, 95% CI 2.00–5.58). ROC analysis demonstrated an AUC of 0.62. LR+ was found to be 2.26 and LR− was 0.70.

**Multivariate analysis**

We performed multivariate analysis in a model which included age, gender, platelet count, ESR, CRP, NLR and

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.011 (0.982–1.041)</td>
<td>0.465</td>
</tr>
<tr>
<td>Number of female gender</td>
<td>1.124 (0.606–2.084)</td>
<td>0.710</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate ≥50 mm/h</td>
<td>2.005 (1.004–4.002)</td>
<td>0.049</td>
</tr>
<tr>
<td>C-reactive protein ≥24.5 mg/l</td>
<td>1.587 (0.806–3.124)</td>
<td>0.182</td>
</tr>
<tr>
<td>Neutrophil-to-lymphocyte ratio ≥9.35 x 10^9/L</td>
<td>1.447 (0.743–2.820)</td>
<td>0.277</td>
</tr>
<tr>
<td>Monocyte-to-lymphocyte ratio ≥0.70 x 10^9/L</td>
<td>0.962 (0.480–1.926)</td>
<td>0.913</td>
</tr>
<tr>
<td>Platelets ≥400 x 10^9/L</td>
<td>3.187 (1.721–5.902)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Observations used: 347; GCA negative: 268, GCA positive: 79. CI, confidence interval; OR, odds ratio.
MLR. We included platelets instead of PLR as it was a stronger predictor in univariate analysis and because there was significant concordance between these two variables. The complete analysis is demonstrated in Table 2. In this model only ESR and platelet level demonstrated a statistically significant association with a positive biopsy result.

**Discussion**

GCA is classified as a medium and large vessel vasculitis, which has the potential to cause permanent blindness secondary to anterior ischaemic optic neuropathy. Although clearly autoimmune, the underlying aetiology of the disease has been debated and is currently unknown.1,3 This inflammatory disorder is most prevalent in patients over the age of 50,2 three times more likely to affect females,15 and may have a higher incidence in some racial groups.18

The American College of Rheumatology established criteria for the diagnosis of GCA,13 requiring the presence of three out of five criteria for a positive diagnosis. These comprise an abnormal temporal artery biopsy (with the presence of monocytic or granulomatous inflammation), age of greater than or equal to 50 years at onset, new onset headache, elevated ESR (greater than or equal to 50 mm/h) and temporal artery abnormality upon physical examination.13

Temporal artery biopsy is considered the best single test and therefore the gold standard investigation for patients with suspected GCA.19,20 Although, there is high specificity (essentially 100% as it is the gold standard in patients with suspected disease), there is a lower sensitivity with reports of between 15% and 40% of temporal artery biopsies being negative in otherwise typical GCA.20 This elevated false negative rate has been attributed to many factors, including the duration of steroid treatment prior to the biopsy, small length of temporal arteries undergoing biopsy and skip lesions.20 Therefore even in patients undergoing biopsy, it is important to note that some patients with negative biopsies may have GCA.21

We performed the first study examining the association between complete blood count (CBC) results and GCA. The NLR, PLR and MLR are ratios derived from the CBC that have been extensively investigated in other disease processes, particularly as a prognostic value in cancer where an elevated NLR predicts a poor prognosis.16,22 There have been limited studies investigating the NLR in vasculitides. Ha et al.13 found that a higher NLR was associated with an adverse prognosis in Kawasaki disease, whilst Ozturk et al.14 demonstrated an association between NLR > 1.29 and Behcet disease.

The results of our study suggest that the NLR and PLR have comparable diagnostic accuracy to traditional ESR and CRP for GCA. Whilst the possible mechanism of this association is unclear, a translational study by Nadkarni et al.23 demonstrated a suppressive neutrophil effect on T-cell proliferation in early GCA, indicating potential involvement of neutrophils in GCA pathogenesis.

It is likely that NLR lost statistical significance in multivariate analysis only because of the strong concordance between NLR, CRP, ESR and platelets – all of which are biological markers of systemic inflammation. It is interesting to note that CRP also lost statistical significance in this model despite its well-established role in GCA diagnosis.1,24

Compared to other studies in the field, we examined a very large cohort of patients (537) who underwent temporal artery biopsy – significantly larger than most studies examining ESR or CRP.21 Furthermore we performed a consecutive series, without any exclusion of patients during the recruitment period and we are confident in the generalisability of the study as patients were recruited from over five centres, including both tertiary and community hospitals.

Although we attempted to minimise this by only collecting data from the first blood test taken during the same admission, but before temporal artery biopsy was performed, it is possible that some of our patients may have already had steroid treatment before the blood for the CBC had been collected. This is of interest because corticosteroid-induced leucocytosis may be a confounding factor in our analysis of the NLR, MLR and PLR results.25 However we suspect that given all patients in the study had sufficient clinical suspicion to warrant temporal artery biopsy, medical management between cases and controls would likely be the same and therefore corticosteroids are unlikely to be a confounding factor.

Overall, based on the likelihood ratios, a raised NLR and PLR is associated with slight increase on post-test probability of GCA whilst a normal NLR and PLR is associated with slightly decreased post-test probability of GCA. As a result, the authors do not suggest that elevations in either NLR or PLR be a strong indication for temporal artery biopsy – rather it should be used as a complementary diagnostic tool that is inexpensive and already ubiquitously tested in cases where suspicion of GCA is equivocal.

**Conclusion**

The PLR and NLR are easily derived from the CBC and therefore widely available at essentially no extra cost in
patients with suspected GCA. Both the PLR and NLR are powerful and statistically significant predictors of a positive biopsy in patients with suspected GCA and can therefore serve as a useful clue in this challenging differential diagnosis.

References


Acknowledgement

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Full blood count in giant cell arteritis
Barriers to medication adherence and links to cardiovascular disease risk factor control: the Framingham Heart Study

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Key words
medication adherence, cardiovascular diseases, hypertension, cholesterol, diabetes mellitus, Type 2.

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Abstract
Background: In the elderly, impaired cognition may weaken medication adherence and compromise treatment for cardiovascular disease (CVD).
Aim: We examined risk factors for medication adherence and the relationship between adherence and levels of CVD risk factors among older participants with hypertension, dyslipidaemia and diabetes in the Framingham Heart Study.
Methods: The four-item Morisky Medication Adherence Scale was administered to 1559 participants, median age 70 years, 53% women. We created an adherence score, ranging from 0 to 4, with low adherence defined as a score ≥2. CVD risk factors were assessed using standard protocols. Cognition was measured using the Mini-Mental State Examination (MMSE) and depressive symptoms were measured using the Center for Epidemiologic Studies of Depression (CES-D) scale.
Results: Among participants who self-reported taking antihypertensive, lipid-lowering and/or hyperglycaemic medication(s), 12% (n=191) had low medication adherence. The risk of low adherence increased by 45% (95% confidence interval (CI): 25–68%, P<0.001) per five-unit increase in CES-D score. In participants taking antihypertensive medication (n=1017), low adherence was associated with higher mean diastolic blood pressure (73 mmHg, 95% CI: 71–75 vs 71 mmHg, 95% CI: 70–71; P=0.04) after adjusting for covariates. Among participants taking lipid-lowering medication (n=937), low adherence was associated with higher mean low-density lipoprotein cholesterol (92 mg/dL, 95% CI: 87–96 vs 86 mg/dL, 95% CI: 84–88; P=0.03). Low adherence was not associated with fasting plasma glucose (P=0.10) or haemoglobin A1c (P=0.68) in the subgroup of participants (n=192) taking hypoglycaemic medication.
Conclusions: Depressive symptoms might act as a barrier for medication adherence, which exacerbates CVD risk factors in older-aged adults.

Introduction
Medication adherence is vital for long-term healthcare expenditure.1,2 Low medication adherence may account for up to $300 billion of annual healthcare costs in the United States.3 It has been estimated that up to 50% of patients do not adhere to prescribed medications, defined as taking fewer doses than prescribed or discontinuing treatment.4–7 Low medication adherence may compromise the effectiveness of treatment for cardiovascular conditions, such as hypertension,8,9 dyslipidaemia10,11 and hyperglycaemia.12,13 However, a systematic review of randomised controlled trials of medication adherence interventions concluded that most strategies aimed at improving medication adherence have not been successful in improving adherence and clinical outcomes for cardiovascular diseases (CVD) and associated risk factors.14 This highlights the need to identify risk factors contributing to
low medication adherence and how low adherence affects CVD risk among high-risk populations.15

Older adults constitute a high-risk population for poor medication adherence; as the population ages, chronic coexisting conditions coupled with decreased cognitive functioning might lead to decreased adherence.7,16,17 A recent systematic review of 15 studies concluded that individuals with cognitive impairment had lower rates of medication adherence compared to those without cognitive impairment.17 Furthermore, the Cohort Study of Medication Adherence among Older Adults (CoSMO), a prospective cohort study of 2194 older adults with hypertension, examined the barriers to antihypertensive adherence and clinical outcomes.16 Participants with low compared with high cognitive functioning were 2.71 times more likely to have low medication adherence and 1.20 times more likely to have uncontrolled blood pressure.16 However, a large gap of knowledge exists regarding risk factors for poor medication adherence and the clinical implications of medication non-adherence on chronic diseases in older adults, particularly those at risk for cognitive decline.7

The objectives of the present study were to: (i) examine risk factors (demographic, socio-economic, lifestyle and cognitive factors) associated with medication adherence; and (ii) study the cross-sectional associations between medication adherence and levels of CVD risk factors among participants with hypertension, dyslipidaemia and diabetes in a sample of older adult participants enrolled in a large community-based cohort. Our hypothesis was that low medication adherence would be common and associated with adverse CVD risk factor profiles.

Methods

Study sample

Framingham Heart Study (FHS) participants who attended the ninth examination (2011–2014) in the Offspring cohort were included. This cohort has been described elsewhere.16,19 Data were collected during a physician interview, a physical examination and by standard laboratory tests for CVD risk factors. The four-item Morisky Medication Adherence Scale20 was administered to the 2430 participants who attended the ninth examination. The use of hypertensive, lipid-lowering and/or hypoglycaemic medication(s) was determined by self-report. After excluding 537 participants who did not report taking at least one of the three studied medications (antihypertensive, lipid-lowering or hypoglycaemic), 245 participants with missing responses to the Morisky Medication Adherence Scale and 89 participants with missing information to covariate assessment(s), a sample, including 1559 participants was available for analysis. The first analysis aimed to study risk factors for low medication adherence. The second analysis studied the associations between medication adherence and CVD risk profiles in 1017 participants taking hypertensive medications, 937 participants taking lipid-lowering medication and 192 participants taking hypoglycaemic medication, with each condition analysed separately. The FHS protocols and procedures were approved by the Institutional Review Board for Human Research at Boston University Medical Center and all participants provided written informed consent.

Medication adherence assessment

Medication adherence was assessed using the four-item Morisky Medication Adherence Scale, which has been used to study adherence for hypertension,20 diabetes21,22 and CVD medications. The four questions included: (i) Did you ever forget to take your medicine? (ii) Are you careless at times about taking your medicine? (iii) When you feel better do you stop taking your medicine? (iv) Sometimes if you feel worse when you take the medicine, do you stop taking it? Response options to these four questions were either yes or no and were assigned the values of 1 or 0 respectively. The values were summed to create an adherence score, ranging from 0 to 4, with higher scores indicating poorer medication adherence. Participants with an adherence score of ≥2 were defined as having low medication adherence, which is consistent with prior studies.21,22

CVD risk factors assessment

At the study examination visit in the FHS research clinic, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG) and haemoglobin A1c (HbA1c) were measured in accordance with standard protocols.24 SBP and DBP were measured twice by the same physician and the average of the two measurements was used. Hypertension (HTN) was defined as SBP ≥140 mmHg, DBP ≥ 90 mmHg or the use of antihypertensive medication. HTN control was defined as SBP < 140 mmHg and DBP < 90 mmHg among participants with HTN. Low density lipoprotein cholesterol (LDLc) was estimated using the Friedewald equation.25 LDLc control was defined as LDLc < 100 mg/dL (2.59 mmol/L) if participants had prevalent CVD or Type 2 diabetes or <130 mg/dL (3.36 mmol/L) otherwise.
Anthropometry and covariate assessment

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Participants who reported that they smoked regularly (on average one cigarette or more per day) in the past year were categorised as current smokers. Alcohol consumption was estimated by self-reported intake of beer, wine, liquor and spirits. A physical activity score was calculated using responses to a questionnaire on the intensity of and time spent performing physical activity per day. Employment status (employed, self-employed or retired from usual occupation vs unemployed or laid off) and marital status (married, living as married or living with partner vs single, never married, separated, divorced or widowed) were derived from a standard questionnaire. The Mini-Mental State Examination (MMSE), a brief dementia-screening questionnaire, was implemented to assess participants’ cognitive function. The MMSE, which has a maximum score of 30, included 16 individual questions to assess functions for orientation, registration, attention and calculation, recall and language and praxis. The Center for Epidemiologic Studies of Depression (CES-D) scale was administered to assess depressive symptoms. The CES-D scale, ranging from 0 to 60, consisted of 20 items evaluating depressive affect, somatic complaints, positive affect and interpersonal relations.

Statistical analysis

The characteristics of participants were calculated by level of adherence, low (adherence score ≥ 2) or high (score < 2) and compared using Student t-test or Chi-squared test. To assess factors associated with low medication adherence, a multiple regression model was implemented with the outcome of low medication adherence. Factors examined included sex, age, BMI, alcohol consumption, current smoking status, physical activity score, employment status, marital status, MMSE score and CES-D score.

Two models were used to examine the associations between low medication adherence and CVD risk factors for each of the self-reported medication groups (antihypertensive, lipid-lowering and hypoglycaemia, separately). Covariates in model 1 were sex and age, while model 2 adjusted for sex, age and variables that were significant in the above analysis for risk factors of low medication adherence. Among participants who reported taking antihypertensive medication, the associations between medication adherence and SBP, DBP and HTN control were analysed. In participants who reported taking lipid-lowering medication, the associations between medication adherence and LDLc and LDLc control were analysed. In participants who reported taking hypoglycaemic medication, the associations between medication adherence and FPG, HbA1c and diabetes control were analysed. Multivariable-adjusted linear regression models were used for continuous outcomes, while Poisson regression models with robust standard errors were used to calculate relative risk (RR) for dichotomised disease control as the prevalence was high.

A secondary analysis was conducted to examine whether age modified the observed association between medication adherence and CVD risk factors. A cross-product term of age (≤70 years or >70 years) and medication adherence was included in the fully adjusted model. An age of 70 years was chosen as it was the median age of the overall study sample. All statistical analyses were conducted using SAS statistical software (version 9.3; SAS Institute, Cary, NC, USA). A two-tailed P < 0.05 value was considered statistically significant.

Results

Participant characteristics

Among the 1559 participants (median age 70 years, 53% women) with complete responses to the Morisky Medication Adherence Scale and covariate assessments, 695 (45%) participants reported that they had forgotten to take medicine; 158 (10%) participants reported that they had been careless at times about taking medicine; 45 (3%) participants reported that they had stopped taking medicine when they felt better and 116 (7%) participants reported that they had stopped taking medicine when they felt worse. Overall, 191 (12%) participants had low medication adherence, defined as adherence score < 2. Among the participants in the low medication adherence group, 181 (95%) reported that they had forgotten to take medicine; 136 (71%) reported that they had been careless at times about taking medicine; 31 (16%) reported that they had stopped taking medicine when they felt better and 73 (38%) reported that they had stopped taking medicine when they felt worse. The prevalence of myocardial infarction and stroke was similar in participants with low medication adherence compared with those with better adherence, 8.4% (n = 16) vs 8.0% (n = 175). Participants with low medication adherence had a higher CES-D score (Table 1; P < 0.001).

Potential risk factors for low medication adherence

As presented in Table 2, higher CES-D scores, indicating more depressive symptoms, were associated with an
increased likelihood of low medication adherence; the odds ratio (OR) for having an adherence score ≥ 2 was 1.44 (95% CI: 1.23–1.67, P < 0.001) for every five-unit increase in CES-D score after adjustment for multiple covariates (Table 2).

In a post hoc analysis, we categorised participants by CES-D score using cut-off values of 16 and 22. We employed a multiple regression analysis that adjusted for all other potential risk factors shown in Table 2. We observed a dose–response relationship between CES-D score and medication adherence. Using participants with a CES-D score below 16 as reference, the OR of low medication adherence was 1.29 (95% CI: 0.91, 1.85) in participants who had a CES-D score of 16–21, while the OR of low medication adherence was 3.03 (95% CI: 1.94, 4.73) in participants who had a CES-D of 22 or above (indicating more severe depression), P-trend < 0.001.

### Table 1: Participant characteristics by self-reported medication adherence (n = 1559)

<table>
<thead>
<tr>
<th></th>
<th>High medication adherence</th>
<th>Low medication adherence†</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>1368 (88)</td>
<td>191 (12)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 ± 8</td>
<td>70 ± 9</td>
<td>0.10</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>712 (52)</td>
<td>111 (58)</td>
<td>0.12</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29 ± 5</td>
<td>29 ± 6</td>
<td>0.46</td>
</tr>
<tr>
<td>Alcohol (servings/week)</td>
<td>5 ± 8</td>
<td>5 ± 7</td>
<td>0.42</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>87 (6)</td>
<td>14 (7)</td>
<td>0.61</td>
</tr>
<tr>
<td>Physical activity score</td>
<td>35 ± 6</td>
<td>35 ± 5</td>
<td>0.67</td>
</tr>
<tr>
<td>Employment, n (%)</td>
<td>615 (45)</td>
<td>82 (43)</td>
<td>0.60</td>
</tr>
<tr>
<td>Marital status, n (%)</td>
<td>405 (30)</td>
<td>70 (37)</td>
<td>0.05</td>
</tr>
<tr>
<td>MMSE score‡</td>
<td>29 ± 2</td>
<td>29 ± 2</td>
<td>0.30</td>
</tr>
<tr>
<td>CES-D score††</td>
<td>15 ± 4</td>
<td>17 ± 5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Numbers in the table are the mean ± standard deviation or proportion (counts). †Low medication adherence was defined as Morisky Medication Adherence Scale score of ≥2. ††Employment status: % unemployed or laid off. ‡Marital status: % single, never married, separated, divorced or widowed. ¶CES-D, The Center for Epidemiologic Studies of Depression. ¶¶MMSE, Mini-Mental State Examination.

### Table 2: Odds ratios for low medication adherence in 1559 Framingham Heart Study participants

<table>
<thead>
<tr>
<th></th>
<th>Multiple regression†</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.07 (0.77–1.50)</td>
<td>0.68</td>
</tr>
<tr>
<td>Age†</td>
<td>0.86 (0.69–1.06)</td>
<td>0.16</td>
</tr>
<tr>
<td>MMSE score‡</td>
<td>1.03 (0.93–1.13)</td>
<td>0.61</td>
</tr>
<tr>
<td>BMI</td>
<td>1.00 (0.98–1.03)</td>
<td>0.78</td>
</tr>
<tr>
<td>CES-D score††</td>
<td>1.44 (1.23–1.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Marital status††</td>
<td>1.34 (0.96–1.88)</td>
<td>0.09</td>
</tr>
<tr>
<td>Unemployed‡‡</td>
<td>0.96 (0.69–1.33)</td>
<td>0.79</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>1.00 (0.97–1.02)</td>
<td>0.72</td>
</tr>
<tr>
<td>Physical activity score</td>
<td>1.00 (0.97–1.03)</td>
<td>0.98</td>
</tr>
<tr>
<td>Current smoking status</td>
<td>1.02 (0.56–1.89)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Numbers in the table are odds ratios (95% CI). Low medication adherence was defined as Morisky Medication Adherence Scale score of ≥2. †Multiple regression model adjusted for sex, age and CES-D score. ††Per 10-year increase in age. ‡‡MMSE, Mini-Mental State Examination. ‡Per 5-unit increased in the Center for Epidemiologic Studies of Depression (CES-D) score. ††Marital status: % single, never married, separated, divorced or widowed. ‡‡Employment status: % unemployed or laid off. BMI, body mass index; CI, confidence interval.

**Participants taking antihypertensive medication (n = 1017)**

Compared with participants who had high medication adherence (n = 918, 90%), those with low medication adherence (n = 99, 10%) had higher DBP after adjustment for sex, age and CES-D score (73 mmHg, 95% CI: 71–75 vs 71 mmHg, 95% CI: 70–71; P = 0.04) (Table 3, top panel). No association was present between medication adherence and SBP or medication adherence and HTN control (Table 3, top panel).

**Participants taking lipid-lowering medication (n = 937)**

Compared with participants who had high medication adherence (n = 825, 88%), those with low medication adherence (n = 112, 12%) had higher LDLc (92 mg/dL, 95% CI: 87–96 vs 86 mg/dL, 95% CI: 84–88; P = 0.03), after adjustment for sex, age and CES-D score (Table 3, middle panel). Participants with low medication adherence were also 11% more likely to have uncontrolled LDLc levels compared to their counterparts in the high medication adherence group (RR: 1.11, 95% CI: 1.02–1.22; P = 0.02) (Table 3, middle panel).

**Participants taking hypoglycaemic medication (n = 192)**

Compared with the high medication adherence group (n = 169, 88%), participants with low medication adherence (n = 23, 12%) showed no statistically significant
differences in FPG, HbA1c or diabetes control (Table 3, bottom panel).

### Secondary analysis

Age-specific analyses for the association between adherence and cardiovascular risk factors and disease control are presented in Tables S1 and S2 (Supporting Information) respectively. The *P*-value for interaction between age and medication adherence was greater than 0.05 for all outcomes except LDLc control and FPG. High adherence was associated with lower LDLc and LDLc control among participants ≤70 years, but not among those >70 years (*P*-interaction = 0.007; Table S2, middle panel). Additionally, the *P*-interaction was 0.05 for FPG (Table S1, bottom panel); however, there was no statistically significant association between medication adherence and FPG levels in either age group.

### Discussion

#### Principal findings

Among older adults in the current analysis, 12% were categorised as having low medication adherence. A higher CES-D score (i.e. more depressive symptoms) was associated with low medication adherence. Furthermore, low adherence was associated with higher DBP in participants using antihypertensive medication and higher and uncontrolled LDLc in participants using lipid-lowering medications.

### In the context of the current literature

The prevalence of low medication adherence in our study sample (12%) is lower compared to several other cohort studies. Nevertheless, our findings are in line with many studies, which have shown that low medication adherence may hinder the effectiveness of treatment for various conditions. For example, low medication adherence is one of the key risk factors for poor hypertension control, and may account for up to half of resistant hypertension cases. CoSMO, including 2194 adults with hypertension, assessed the determinants of medication adherence using the medication possession ratio and a validated self-report adherence scale. The analyses showed that adherence, measured by both metrics, was associated with uncontrolled blood pressure. It should be noted that high SBP is particularly prevalent among adults in FHS, which might have

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### Table 3 Cardiovascular risk factors and disease control by self-reported medication adherence

<table>
<thead>
<tr>
<th></th>
<th>High medication adherence</th>
<th>Low medication adherence</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals using antihypertensive medication (n = 1017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)†</td>
<td>Model 1: 918 (90)</td>
<td>99 (10)</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>Model 2: 129 (128, 130)</td>
<td>131 (128, 134)</td>
<td>0.37</td>
</tr>
<tr>
<td>DBP (mmHg)§</td>
<td>Model 1: 71 (70, 71)</td>
<td>73 (71, 75)</td>
<td>0.03*</td>
</tr>
<tr>
<td></td>
<td>Model 2: 71 (70, 71)</td>
<td>73 (71, 75)</td>
<td>0.04*</td>
</tr>
<tr>
<td>HTN control (%)‡§</td>
<td>Model 1: 1.02 (0.91, 1.15)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Model 2: 1.02 (0.91, 1.15)</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

| Individuals using lipid-lowering medication (n = 937) |                           |                          |           |
| LDLC (mg/dL)††‡                  | Model 1: 86 (84, 88)     | 91 (87, 96)              | 0.04      |
|                               | Model 2: 86 (84, 88)     | 92 (87, 96)              | 0.03      |
| LDLc control (%)††§              | Model 1: 1.12 (1.02, 1.22)| 0.01**                |
|                               | Model 2: 1.11 (1.02, 1.22)| 0.02**                |

| Individuals using hypoglycaemic medication (n = 192) |                           |                          |           |
| FPG (mg/dL)‡‡§                 | Model 1: 134 (128, 139)  | 143 (128, 158)           | 0.24      |
|                               | Model 2: 133 (128, 138)  | 147 (132, 162)           | 0.10      |
| HbA1c (%)§§                   | Model 1: 6.8 (6.4, 7.2)  | 6.8 (6.4, 7.2)           | 0.91      |
|                               | Model 2: 6.8 (6.4, 6.9)  | 6.8 (6.4, 7.2)           | 0.68      |
| Diabetes control (%)          | Model 1: 0.87 (0.69, 1.10)| 0.24                    |
|                               | Model 2: 0.86 (0.67, 1.12)| 0.27                    |

Numbers in the table are least squares mean and 95% confidence interval (CI) for continuous variables (SBP, DBP, LDLC, FPG and HbA1c) and relative risk and 95% CI using Poisson regression with robust standard errors for disease control. Model 1 covariates: age and sex. Model 2 covariates: age, sex and CES-D score. Low medication adherence was defined as Morisky Medication Adherence Scale score of ≥2. SBP, systolic blood pressure. DBP, diastolic blood pressure. HTN, hypertension. LDLC, low density lipoprotein cholesterol. FPG, fasting plasma glucose. HbA1c, haemoglobin A1c. *P*-value < 0.05. **P-value < 0.01.
decreased the power for the association between SBP and medication adherence. Additionally, a retrospective cohort study of 1066 patients receiving statin medication found that the risk of not achieving the LDLc reduction goal in patients who had intermediate and low adherence increased by 31% and 88% respectively compared with those with high adherence. Although the present study did not find an association between medication adherence and glycaemic control, potentially due to the small sample size of participants using hypoglycaemic medication (n = 192), other studies have reported an association. In a systematic review of adherence and glycaemic control determined by HbA1c, there was a direct association between low medication adherence, which was assessed by self-report and pharmacy fills, and worse glycaemic control. Many intervention studies have been designed, but failed to improve either medication adherence or associated clinical outcomes through improvements in adherence. Interventions specifically designed to improve medication adherence barriers in individuals at-risk for poor adherence could lead to better clinical outcomes. For example, the observation from the present study that a higher CES-D score could constitute a barrier for adherence is consistent with other studies. To target depression as a barrier to medication adherence for comorbid conditions, studies have analysed the extent to which integrated care could be effective in treating both disease outcomes. A randomised trial in 64 individuals with hypertension and depression showed that integrated care, focused on treating hypertension and depression simultaneously, improved adherence to antihypertensive medications and resulted in lower blood pressure. However, a randomised controlled trial that examined individual cognitive therapies in 94 outpatients with diabetes and comorbid depression found that glycaemic control was not improved even though depressive symptoms were reduced. Thus, future intervention studies tailored to older adults with depression and CVD are warranted to improve medication adherence and clinical outcomes.

It should be noted that other factors in addition to depression may be barriers to achieving high medication adherence. As shown in the present analyses, adjustment for depressive symptoms did not substantially change the association between low medication adherence and increased CVD risk. Cognitive impairment and memory may have a role in medication adherence among the elderly. MMSE score ceiling effects resulted in no statistically significant association between cognitive functioning and low medication adherence in the present study. The MMSE alone may not be effective in diagnosing mild cognitive impairment. Nevertheless, a small pre–post intervention study found that reminder devices improved medication adherence in older adults with mild cognitive impairment. Thus, additional well-designed studies with larger sample sizes are needed to identify the role of cognitive decline in medication adherence, as well as the relationship between reduction of these factors and control of chronic diseases in the elderly population.

Implications

Many studies have shown that medication adherence is an important factor associated with CVD risk. Although, the observed association is relatively weak, our findings do support that improving medication adherence may benefit control for CVD risk factors. This is particularly important for the elderly population since older adults constitute a high-risk population for poor medication adherence due to decreased cognitive function. The finding that depressive symptoms may act as a risk factor for medication non-adherence in older adults should be considered in future intervention studies and clinical practice.

Strengths and limitations

This study used the comprehensive data collected from FHS, which has been a hallmark in identifying CVD risk factors among free-living adults. However, due to the observational and cross-sectional nature of this study and relatively weak observed association between medication adherence and CVD risk factors, a causal relationship could not be ascertained. No gold standard definition exists for long-term medication adherence. Defining low medication adherence as two or more positive responses to the Morisky Medication Adherence Scale is somewhat arbitrary and primarily focuses on participants' attitudes toward their medications rather than their behaviours. The self-reported questionnaire also has the potential to introduce response bias into the study. In addition, the Morisky Medication Adherence Scale does not assess other factors that may contribute to low medication adherence, such as the general healthcare system. We could not validate medication adherence assessed by the questionnaire with medication possession ratios or provider data in our study sample. Furthermore, since only one medication adherence questionnaire was implemented, we cannot test the association of current CES-D score to remote medication adherence. The use of MMSE to measure cognitive functioning might not have been sufficient to identify those with mild cognitive impairment, especially because previous studies have found that cognitive impairment significantly impacts medication adherence.
secondary age interaction analyses were also limited due to the small subgroup sample sizes. Finally, all study participants were Caucasian, which may limit the generalisability to populations of different racial and/or ethnic backgrounds.

**Conclusion**

Low medication adherence was associated with adverse CVD risk profiles, including uncontrolled LDLc and higher DBP and LDLc, in a group of older adults in the community. Having more depressive symptoms was associated with low medication adherence. Future intervention studies are warranted to examine if integrating care for depression and CVD risk factors could improve medication adherence and clinical outcomes in the elderly.

**Acknowledgements**

This work was conducted in part using resources and data from the Framingham Heart Study (FHS) of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institute of Health and Boston University School of Medicine.

**References**

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Medication adherence and CVD risk

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

**Table S1.** Age interaction for cardiovascular risk factors by self-reported medication adherence.

**Table S2.** Age interaction for relative risk of uncontrolled disease by self-reported medication adherence.
A description of ‘Australian Lyme disease’ epidemiology and impact: an analysis of submissions to an Australian senate inquiry

Jeremy D. Brown 1,2,3

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Key words
Lyme, chronic, media, antibiotic, fibromyalgia.

Abstract

Background: Many Australian patients are diagnosed and treated for the scientifically and politically controversial diagnosis of an endemic form of ‘Australian Lyme Disease’. Patient advocacy led Senator John Madigan to propose an Australian Senate Inquiry into this illness.

Aim: To describe the symptomology and outcomes of patients diagnosed and treated with Lyme disease in Australia.

Methods: All public, first-person submissions (n = 698) to the inquiry were reviewed and responses analysed for epidemiology, symptoms and impact against structured criteria.

Results: The most common symptoms described were fatigue (62.6%), disordered thinking (51.9%) and sensory disturbance (46.1%). Respondents reported experiencing symptoms for a median of 10 years and spent a median of $30 000 on diagnosis and treatment. Almost 10% of respondents self-diagnosed after being exposed to a media report of Australian Lyme disease.

Conclusions: Patients diagnosed with Lyme disease in Australia display a symptomology similar to ‘medically unexplained physical symptoms’ syndromes, experience social and financial harms, and are at risk of nosocomial harms. Negative medical interactions and the media may contribute to patients seeking alternative and potentially non-evidence-based diagnoses and treatments.

Introduction

Lyme disease is a tick-borne bacterial infection caused by Borrelia burgdorferi sensu lato, endemic in North America and Europe. In Lyme-endemic areas, controversy exists regarding a post-treatment syndrome or ‘chronic Lyme disease’ characterised in general by fatigue, cognitive disturbance and joint pain.1–3 Several trials show that protracted antibiotic therapy, even in the context of proven and successfully treated Lyme disease, does not offer benefit.2,3

In Australia endemic ‘Australian Lyme disease’ has been controversial for at least 30 years.4 The issues surrounding ‘Australian Lyme disease’ have been reviewed recently and recommendations for diagnosis have been published.1–6 There is no current evidence of B. burgdorferi sensu lato in non-travelling Australian patients or Australian ticks.5,6–11

However, there are patient advocacy groups and some doctors in Australia that describe, diagnose and treat an Australian ‘Lyme-like illness’. Australian Lyme disease has featured in the media, with at least 13 television reports in 2012 alone.12 The Australian Government convened a Clinical Advisory Committee on Lyme Disease and Lyme disease ‘round table’ in 2013–2014 which suggested the need for more research and ongoing investigation.13 On 12 November 2015, at the request of Independent Senator John Madigan, a Senate inquiry was convened into the ‘Growing evidence of an emerging tick-borne disease that causes a Lyme like illness for many Australian patients’.14 Submissions could be public, anonymous or confidential to the inquiry and the terms of reference included ‘the signs and symptoms Australians with Lyme-like illness are enduring and the treatment they receive from health professionals’.14 Lyme advocacy groups requested sufferers make

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Conflict of interest: None.
personal stories of 698 people who self-identified as having Lyme disease in Australia. Often, these diagnoses and treatments rely on tests from laboratories in Australia and overseas that are not accredited by the National Association of Testing Authorities (NATA) or the Royal College of Pathologists of Australasia (RCPA). Analysis of these submissions provides insight into the symptomology, diagnosis, treatment and social circumstances of self-identified Lyme disease sufferers in Australia.

Methods

All public submissions to the Senate inquiry were appraised. Submissions from patients identifying as suffering from Lyme disease or Lyme-like illness were included.

Data collected included patient age, sex, potential location of acquisition, history of tick bite, symptoms, diagnostic laboratory tests, treatment, behaviour of health professionals, and financial and social costs. For criteria where a range was reported, (e.g. expenses) the minimum figure was included for analysis.

Reported symptoms included ‘disordered thinking’ (including ‘brain fog’, ‘memory loss’ or loss of mental acuity) and ‘seizures’ as described by the patient.

‘Diagnosis based on media included’ reports of a direct causation between a media report and self-recognition of Australian Lyme-like illness. ‘Self-diagnosis based on internet’ includes reports of either generating or confirming a suspicion of Lyme disease based on internet use. ‘Co-infections’ refer to other tick-borne infections contracted at the time of tick bite that for some pathogens can exacerbate classical Lyme disease.

Reports of antibiotic treatment not specifying the route were included in the oral group. To meet the criteria for having ‘negative medical interaction’ the submission must have reported an undesirable outcome in addition to simple disagreement regarding diagnosis.

Only direct costs of investigation and treatment were included, potential lost income was excluded, as were recurring costs without a specific time frame. Patients who sought medical advice overseas, including by video conference, were included as ‘treated overseas’. Only spousal relationships were included for relationship breakdown.

Results

The inquiry received 1266 submissions in total and published 698 eligible submissions, 54.6% from females, 13.3% from males and 32.1% from patients who did not disclose their sex, with a median age of respondents of 44 years. The epidemiology, management and impacts of a diagnosis are described in Table 1. The symptoms described by respondents are listed in Table 2. Of 68.3% of submissions that reported a location of acquisition, only 9.5% reported this as overseas. Over half (58.8%) of submissions did not comment on tick bite, but of those that did, a majority (89.5%) reported a positive history.

The median duration of symptoms was 10 years. Of submissions that reported at least one symptom, the mean number reported was 5.7. The most prevalent symptom was fatigue, followed by disordered thinking. 348 (49.9%) submissions mentioned antibiotic therapy, only two patients denied using any antibiotics.

Of the total patients, 10.5% reported another diagnosis that could explain their physical symptoms, including multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Crohn’s disease and motor neuron disease (MND).

Of 137 submissions that disclosed a NATA/RCPA-accredited diagnostic pathology test, only 14 (10.2%) reported positive serology (representing 2.8% of all that reported pathology and 2.0% of all submissions). Ten patients had travelled overseas, and the four other patients who either had not travelled or did not mention travel did not report the result of confirmatory (Western blot) serological testing. Two patients reported that they had contracted Lyme disease overseas (USA and France), and another two patients who reported travel also reported explicitly that only first-tier testing was positive.

Respondents had seen a median of 13 doctors for diagnosis and treatment of their illness. Experiences of traditional healthcare were overwhelmingly negative, with 395 (56.6%) submissions reporting negative interactions and only 13 (1.9%) exclusively positive.

In general, the submissions were dismissive of doctors that did not concur with a diagnosis of Australian Lyme disease and highly complimentary to doctors offering treatment. Representative comments include ‘The way I had been treated by the medical fraternity made me feel that my illness wasn’t real and that being sick was my fault due to stress, lifestyle or psychological issues’ and ‘After 7 years, 16 doctors… …and some random spiritual healers, I had a reason, a real diagnosis!! Joy to the world!’.

A negative financial impact was reported in 393 submissions (56.3%) and stopping employment or education by 352 (50.4%).

Discussion

The submissions to an Australian Senate inquiry describe the clinical syndrome of ‘Australian Lyme-like illness’ and its similarity to other ‘medically unexplained physical
syndrome’ (MUPS) disorders, and in particular highlight the social and financial harms associated with diagnosis and treatment. However, submissions unquestionably detail real and debilitating physical and social harm from illness, regardless of aetiology, with many suffering for many years (the median duration of symptoms was 10 years). Over half reported significant financial hardship (56.2%, with a median cost of treatment of $30 000) or stopping employment or education (50.4%), with 8% also reporting spousal relationship breakdown. Submissions had a striking female preponderance (80.3% when reported). The most commonly reported symptoms were fatigue, disordered thinking or ‘brain fog’, arthralgia and myalgia, sensory disturbance and headache. Both the female skew and these symptoms are prominent components of both fibromyalgia and chronic fatigue syndrome (CFS), the two most prominent MUPS disorders. In endemic areas, Lyme disease has a slight male preponderance, most likely attributable to males being more likely to engage in at-risk occupations or hobbies.

Only a small minority of patients reported a positive Lyme disease serology test from a NATA/RCPA accredited laboratory. A proportion of these may be positives from overseas exposure unrelated to their current illness, and some may represent only positive first-tier testing and not confirmatory testing as required by the RCPA position statement on laboratory testing for Lyme disease.
The non-specific symptoms, female preponderance and lack of confirmatory laboratory testing, suggest that these patients are more likely to be experiencing a MUPS disorder (such as CFS) than an active or latent infection. The same conclusion has been reached by investigators of ‘chronic Lyme disease’ in the USA that actively compared healthy, CFS and ‘alternatively diagnosed Lyme’ groups. Consistent with this conclusion, antibiotic therapy is not effective in the treatment of ‘chronic Lyme disease’.2,3

The vast majority of the antibiotics prescribed to respondents are likely to have been inappropriate, with the potential to cause harms from both side-effects and antimicrobial resistance. There are documented harms associated with long-term antibiotic treatment of chronic Lyme disease, including from unnecessary intravenous access, which has been associated with deaths.22,23 An additional potential harm is missed diagnoses and treatment of concurrent serious illnesses, as has been described for cancers in Australia and overseas.24 In this study, 10.5% of submissions reported a previous significant diagnosis, such as RA, SLE, MND or MS.

While not captured in this analysis beyond the financial costs, others have documented the significant range and potential harms of non-mainstream approaches to treating ‘chronic Lyme disease’.25,26

Patients with MUPS disorders are frequently frustrating for clinicians to treat and this frustration may contribute to negative medical interactions, frequent referral and seeking multiple opinions.17 One potential issue is that in the absence of a clear diagnosis, a clinician may feel they can only offer ‘affectionate reassurance’ (non-specific reassurance based on rapport), which has been suggested to be less durable and effective than ‘cognitive reassurance’ (changing patients’ perceptions and beliefs through education).27 Cognitive reassurance delivered in a non-judgemental manner to patients with MUPS disorders contemplating an Australian Lyme disease diagnosis may help prevent reliance on this diagnosis, allow beneficial MUPS-directed therapy, and prevent the very real social and financial hardship associated with diagnosis and treatment of Australian Lyme (see Table 1). While there is variation in the treatment guidelines for MUPS disorders, most focus on education, cognitive behavioural therapy, graded physical exertion and careful titration of pharmacotherapy with CNS modulatory effects, with frequent success – none recommend antibiotics.17,28

Lack of communication and satisfaction from mainstream medical services may also be a contributing factor to another phenomenon highlighted in this study: self-diagnosis of Lyme disease after media reports. Almost 10% of submissions reported self-diagnosis after viewing a media report. Media influence on increasing diagnosis and clinical presentations has been described in influenza and in particular mental health, where media coverage of suicides can lead to increased at-risk presentations and suicides.29,30 A patient who feels let-down by mainstream medicine may personally identify with the generally sensationalised, but ultimately hopeful, tone of many of these media reports, and then seek a similar diagnosis.

Senate submissions fall short of the standards required of a systematic survey of patients definitively to describe symptoms and epidemiology. However, the promotion of the inquiry by Australian Lyme disease advocacy groups, the large number of responses and the use of a standardised format by many respondents means that broadly useful conclusions may still be drawn. A bias towards more politically active, more literate and more severe symptoms is expected. An additional methodological issue is that only one researcher reviewed the submissions, however, minor variations in classification are unlikely to alter significantly the broad nature of the conclusions drawn.

Conclusion

The Senate inquiry submissions are a manifestation of a failure of evidence-based medicine to influence patients and policy, leading to genuine physical, social and financial harm for patients. These patients most likely represent, in general, a cohort of individuals with a MUPS disorder similar to CFS or fibromyalgia. Both the media and medical professionals have a role to play in preventing medical and social harms associated with diagnosis and treatment of non-evidence-based conditions.

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**Trends in outpatient anti-arrhythmic prescriptions for atrial fibrillation and left atrial ablation in Australia: 1997–2016**

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**Abstract**

**Background:** An important aspect of atrial fibrillation (AF) management is the decision whether to adopt a rate or rhythm control strategy. Options for the latter include oral anti-arrhythmic drugs (AAD) or catheter ablation.

**Aim:** To describe the trends in rhythm control for AF in Australia between 1997 and 2016.

**Methods:** We conducted a retrospective study using prospectively collected data between 1997 and 2016 from the Pharmaceutical Benefits Scheme and Medicare Benefits Schedule websites, which, respectively, contain information pertaining to public AAD prescriptions and rebatable AF ablation procedures performed in Australia.

**Results:** Sotalol and amiodarone remain the most commonly prescribed AAD in Australia, although their use is decreasing. Rates of catheter ablation for AF continue to rise annually with a 48-fold increase from 71 to 3480 since 1997.

**Conclusion:** A rhythm control strategy is frequently utilised for AF management in Australia. Consistent with international guidelines which advocate safety over efficacy when choosing a rhythm control strategy, the prescriptions of amiodarone have been consistently decreasing since 2002, whereas sotalol and flecainide prescriptions have largely increased, with a peak in 2015. Catheter ablation per capita has burgeoned 36-fold.

**Introduction**

Atrial fibrillation (AF) is the most common sustained arrhythmia, and is estimated to affect approximately 500,000 individuals in Australia and its prevalence is increasing.1,2 Once diagnosed, key aspects in the management of AF are initiating anti-coagulation in those at high risk of thromboembolism and choosing between a rate or rhythm control strategy. Rhythm control is indicated to improve symptoms in patients with AF, although its use is decreasing. Rates of catheter ablation for AF continue to rise annually with a 48-fold increase from 71 to 3480 since 1997.

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Data are presented as counts or per capita. The data are publicly available and are anonymised and as such, ethical approval was not required for this study.

**Results**

The main findings are illustrated in Figure 1. Between 1997 and 2016 the population of Australia grew by 32% and the population has aged (median age increased from 34.3 to 37.3 years with a doubling in the proportion of persons aged 85 years and older from 0.9 to 2.0%). In this period the total number of AAD dispensed per capita increased by 48.4%; however, the growth in AAD prescriptions markedly slowed down after 2002 and started to decline after 2015. Sotalol is currently the commonest prescribed AAD with a total of 428,468 prescriptions in 2016. Amiodarone prescribing peaked in 2002 at 442,626 and has shown a slow decline with a total of 332,223 prescriptions in 2016. Flecainide prescribing has had a marked threefold increase to a total of 273,338 prescriptions, with peak prescribing in 2015, after which there was a small decline in use (Fig. 1). Over the duration of the study, disopyramide has remained the least prescribed of all four AAD and its use continues to decline. The total cost of AAD prescribing had increased until 2002 before gradually declining to $16,524,516 in 2016.

AF ablation case numbers have increased 48-fold from 71 to 3,480 over the same period (Fig. 1). Patients aged 65–74 years old are now the modal age-group to receive AF ablation (Fig. 2).

**Discussion**

The main findings of this study are that: (i) the growth in AAD use began to slow after 2002 and after 2015 AAD use began to decline; (ii) sotalol remains the commonest prescribed AAD followed by amiodarone and flecainide. Until 2015, the use of sotalol and flecainide was increasing after which their use began to decline; (iii) AF ablation has seen an increase in uptake, throughout all age groups.

**Rate versus rhythm control**

A diagnosis of AF as compared to sinus rhythm has deleterious consequences and is associated with an increased risk of death, stroke, hospitalisation, heart failure, cognitive decline and reduced quality of life. However, three large randomised controlled clinical trials of ‘rate versus rhythm’ strategy have failed to show any benefit of a rhythm control strategy on mortality or composite endpoints. A decline in AAD prescriptions followed the initial publications in 2002, which are mirrored by our data. The interpretation of these ‘rate versus rhythm’ trials has been debated. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study was the largest of the three trials. It highlighted that contemporary AAD had variable efficacy with 62.6% of the rhythm control arm of AFFIRM in sinus rhythm at 5 years. Post hoc analyses suggested that those patients who did maintain sinus rhythm during the trial had improved survival; however, this overall effect was
negated by the toxicity associated with AAD. The mean age of the patients in AFFIRM was 70 years and hence the findings might not be applicable to younger patients.

The AFFIRM trial results have not dissuaded cardiologists from attempting to achieve rhythm control in their patients. In a survey of 17 centres across Europe, 60% of patients were offered a rhythm control strategy after the first detected episode of AF as were up to 50% of young and apparently asymptomatic patients. The main limitation is clearly not a lack of desire to achieve rhythm control, rather a lack of tolerable and effective tools.

Which AAD?

Safety rather than efficacy considerations should guide which AAD is prescribed. The reduction in amiodarone prescriptions in Australia is consistent with this tenet. Amiodarone is associated with long-term multi-organ toxicity and should be restricted to symptomatic patients with heart failure or those patients with structural heart disease who fail first-line AAD and/or ablation.

Flecainide has a similar potency as amiodarone in maintaining sinus rhythm and reducing symptoms. Physicians may have been deterred from using this drug in earlier years following the results of the Cardiac Arrhythmia Suppression Trial study in 1991. In this trial, patients with recent myocardial infarction were randomised to either placebo or flecainide/encainide/moricizine (depending on ejection fraction) if they had six or more ventricular premature complexes per hour (not AF). A total of 1468 patients (mean age 61 years, mean ejection fraction 40%) was randomised. The trial had to be stopped prematurely due to a significantly increased risk of death or cardiac arrest seen in the AAD arm (relative risk 2.38, 95% confidence interval: 1.59–3.57). Since this trial, there has been a further 26 years of experience using flecainide to suppress atrial arrhythmias with extensive safety data underpinning its use in appropriately chosen populations. In a meta-analysis of 4811 patients with 2015 patient-years of exposure to flecainide, there was no suggestion of increased mortality associated with the drug. It was on this background that international guidelines have supported the use of this drug in patients with AF but without structural heart disease. In accordance with guidelines, there has been an increase in confidence with this drug in Australia and worldwide.

Sotalol may be used to maintain sinus rhythm in patients with structurally normal hearts and coronary artery disease. In patients with left ventricular hypertrophy, heart failure, prolonged corrected QT-interval (>450 ms) or bradycardia, sotalol is pro-arrhythmic and is associated with torsades de pointes and increased mortality and hence should be avoided. The data suggest that sotalol is less efficacious than amiodarone or flecainide. In light of this, it is unsurprising that the use of sotalol has begun to decrease in Australia. However, limited effective and safe alternatives are available. During the 20 year span of this study, there have been no new AAD licensed in Australia. In Europe and the United States, dronedarone has been available since 2009 to maintain sinus rhythm, however, due to limited efficacy compared to amiodarone and increased risk of harm in specific populations of patients, this drug did not receive approval in Australia.
Disopyramide is now rarely used as it is associated with increased mortality particularly at higher doses.\(^\text{14}\) It may have a niche role in vagally-mediated AF and in patients with hypertrophic cardiomyopathy associated with left ventricular outflow tract obstruction.\(^\text{3}\)

**Catheter ablation**

National and international consensus groups recommend cardiac catheter ablation for AF to improve quality of life where antiarrhythmic therapy has failed to control symptoms.\(^\text{1,3}\) There is growing evidence that first-line pulmonary vein isolation may be an acceptable and effective approach compared to AAD therapy to maintain sinus rhythm\(^\text{19,20}\) despite a reported complication rate of ~2.6%.\(^\text{21}\)

In Australia, there has been a rapid growth in the number of AF ablations performed and this has been mirrored in Europe and the United States.\(^\text{22,23}\) This likely reflects the increasing sentiment that in select patients and in high volume centres, ablation (often combined with AAD) has been shown to be more effective (maintenance of sinus rhythm, improving quality of life and reducing cardiovascular hospitalisation) than long-term AAD.\(^\text{3,4}\) However, at present, there is no evidence that AF ablation (or anti-arrhythmic medication) reduces the risk of stroke, heart failure or death in an unselected population. The Catheter Ablation versus Anti-Arrhythmic Drug Therapy for Atrial Fibrillation (clinicaltrials.gov identifier- NCT 00911508) and Early Treatment of Atrial Fibrillation for Stroke Prevention (clinicaltrials.gov identifier- NCT01288352) trials are in progress to address this question. Recently, however, in patients with heart failure reduced ejection fraction and AF, an ablation strategy compared to pharmacological rate/rhythm therapy has been shown to improve left ventricular systolic function\(^\text{24}\) as well as reduce heart failure hospitalisation and all-cause mortality.\(^\text{25}\)

**Lifestyle management and modifying risk factors to maintain sinus rhythm**

Hypertension, obesity and obstructive sleep apnoea (OSA) are risk factors that independently contribute to the arrhythmogenic substrate that promotes AF and there is growing evidence that targeting these can reduce AF burden.\(^\text{5,26}\)

A meta-analysis of 11 prospective randomised controlled trials found that angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) reduced the relative risk of incident AF by 28% and this effect was most pronounced in those patients with left ventricular systolic heart failure or hypertension associated with left ventricular hypertrophy.\(^\text{27}\) However, the efficacy of these drugs in patients with established AF to prevent recurrence of AF is less clear.\(^\text{28}\) International guidelines support the use of ACEi/ARB for the primary prevention of AF in patients with heart failure, hypertension and post cardiac surgery.\(^\text{4}\)

In patients without cardiovascular diagnoses, the risk of AF increases by 8% with every unit increase in body mass index (BMI).\(^\text{29}\) In individuals with AF and a BMI > 27 kg/m\(^2\), a 10% reduction in weight through a dedicated multi-disciplinary clinic was associated with a six-fold reduction in AF burden.\(^\text{30}\) Furthermore, a randomised controlled trial demonstrated a reduction in AF symptoms in those overweight patients allocated to the weight loss arm.\(^\text{31}\) Guidelines recommend weight loss in obese patients with AF to reduce AF burden and symptoms.\(^\text{3}\)

OSA is associated with the previous two risk factors for AF. OSA is frequently underdiagnosed due to the low sensitivity of the screening questionnaires used and hence clinicians should have a low threshold to request formal sleep studies.\(^\text{32}\) Continuous positive airways pressure in patients with OSA and AF reduces AF burden and improves the efficacy of AAD and catheter ablation used as part of a rhythm control strategy; however, these data are derived from observational studies only and randomised controlled trials are planned (ANZCTR register: ACTRN12616000903482).\(^\text{33}\) Guidelines recommend that sleep studies are conducted in those patients in whom sleep apnoea is suspected and if diagnosed treatment initiated and optimised.\(^\text{3,4}\)

AF rarely occurs in the absence of any concomitant cardiovascular risk factors, historically described as ‘lone AF’.\(^\text{34}\) The management of AF should involve the comprehensive treatment of the risk factors known to create the substrate for maintaining AF.\(^\text{5}\) The Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation (ARREST-AF) cohort study\(^\text{35}\) evaluated the impact of risk factor management on AF ablation outcomes. In this observational case-control study, those patients who chose to receive risk factor management underwent targeted reductions in: (i) blood pressure to <130/80 mmHg; (ii) glycosylated haemoglobin in diabetics to <7%; (iii) low-density lipoprotein to <2.6 mmol/L and triglycerides to <2.6 mmol/L; (iv) weight by 10% or BMI to ≤25 kg/m\(^2\); as well as (v) diagnosis and treatment of OSA if the apnoea-hypopnoea index was ≥30/h (>20/h if there was resistant hypertension); (vi) smoking cessation and (vii) reduction in alcohol consumption to ≤30 g/week. After a mean follow-up of 3.5 years those patients in the risk factor management cohort had a significantly better AF-free survival (32.9% vs 9.7%, \(P < 0.001\)) and this was associated with greater global well-being scores. The
benefits of lifestyle changes and risk factor optimisation upon maintaining sinus rhythm should have a more prominent role in patient encounters.

The future

The prevalence of AF continues to rise, owing primarily to better detection and a changing risk factor landscape, with an ageing population and rising rates of obesity. Current trends in both pharmacological and ablative management of AF suggest that increasing amount of resources will need to be allocated to treat this disease and the cost-benefit ratio as well as risk-benefit profile of current therapies will need to be closely examined. Population level interventions to target risk factors for AF, which include obesity, hypertension, chronic kidney disease, smoking and excessive alcohol consumption will be critical to kerb the AF epidemic. Development of novel AAD and ablation strategies, in combination with substrate prevention, remains a fertile area of research.

Limitations

Our data detail the annual number of prescriptions issued and number of catheter ablations for AF performed, which does not reflect the total number of patients treated in Australia. This does not detract from our findings as we are still able to describe trends in the management of AF in Australia. We limited our study to membrane active oral AAD, which excludes other medications known to maintain sinus rhythm, such as beta-blockers. A confounder in our data is the absence of information on the indication for which the AAD are prescribed. Although the majority of prescriptions were likely for the management of atrial arrhythmia, it is unknown what proportion was used in the management of ventricular arrhythmias.

We used procedural data from the Medicare Australia database, which collects private sector data only, and does not contain public hospital data. In 2011–2012, 42.9% of all people 18 years of age and over did not have private health insurance and so the true frequency of AF ablation is likely to have been underestimated. Estimation of a precise frequency is further confounded by the absence of a specific billing code for AF ablation as the ‘38290’ code may include other arrhythmias, such as left-sided accessory pathways and atypical flutter. However, we would expect the trend in ablations performed to remain valid. We have no data on the strategy (pulmonary vein isolation, left atrial lines, complex fractionated electrogram ablation) or modality (radiofrequency, cryotherapy) used to perform AF ablation.

Conclusion

Rhythm control of AF using AAD and AF ablation has increased over the last two decades (96% and 4800% respectively) in Australia. Clinicians are prescribing less amiodarone and are showing increasing confidence in flecainide, while sotalol remains the commonest prescribed AAD despite safety concerns. It is likely that over the subsequent years the demand for AF ablation will continue to surge, and it remains unclear whether current infrastructure and resources are available to match growing trends.

References

High rates of respiratory symptoms and airway disease in mental health inpatients in a tertiary centre
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Key words
mental illness, COPD, respiratory illness, OSA, sleep apnoea.

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Abstract
Background: People with severe mental illness (SMI) have a lower life expectancy due in part to a higher prevalence of cardiac and metabolic disease. Less is known of the prevalence of respiratory disease in this group.
Aims: This cross-sectional, observational study aimed to assess the prevalence of symptoms associated with respiratory disease in patients admitted to an inpatient mental health unit.
Methods: A convenience sample of 82 inpatients had a structured interview and questionnaire completed. The questionnaire included self-reported diagnoses of common diseases and screening questions designed to detect respiratory disease and sleep disordered breathing. Targeted spirometry was performed on the basis of symptoms and smoking status.
Results: Patients reported high rates of respiratory symptoms, including wheezing (38%) and dyspnoea (44%); 52% of patients reported daily tobacco use. Productive cough was significantly associated with tobacco use ($P < 0.005$). Ten patients (18%) had spirometry consistent with chronic obstructive pulmonary disease (COPD) of whom six did not have a formal diagnosis of COPD previously.
Conclusions: People with SMI have high rates of respiratory symptoms with a high prevalence of COPD on spirometry. Half of the COPD cases were not previously diagnosed, suggesting a hidden burden of respiratory disease in patients with SMI.

Introduction
People with severe mental illnesses (schizophrenia, bipolar disorder and major depression) are at a significantly higher risk than the general population of developing serious physical health conditions that reduce life expectancy. Mental disorders are independently associated with excess all-cause mortality and account for approximately a quarter of the burden of disease both in Australia and globally. Among people with severe mental illness (SMI), medical illness accounts for the majority (87%) of potential years of life lost and for 60–70% of the excess mortality. Cardiovascular disease accounts for approximately 30% of deaths due to medical illness in this group.

Tobacco use is notably higher among people with SMI. Data from the 2010 Australian Survey of High Impact Psychosis found that the prevalence of current tobacco smoking was 66.6%, with a lifetime prevalence of 81%, in contrast to an Australian general population prevalence of 19–21% of adults. In addition to tobacco smoke, cannabis use is common in those with SMI and is likely to have adverse health effects equal to tobacco. Australia has one of the world’s lowest rates of smoking; however, as rates fall, disadvantaged groups, including those with SMI, now comprise a greater proportion of all smokers.

Although there is an awareness of cardiovascular risk in patients with SMI, there is less research relating to the presence of respiratory illness in this group. Patients with SMI are twice as likely to be hospitalised for preventable exacerbations of asthma and chronic obstructive pulmonary disease (COPD) as those without mental illness. Patients with schizophrenia are more likely to die of COPD and to have a higher prevalence of COPD than the general population.

It is likely that there is an underdiagnosis of asthma and COPD in those with SMI. A study of geriatric patients with bipolar disorder (BPD) found a prevalence of COPD of 6%; however, over 50% reported significant
respiratory symptoms or required daily inhalers. COPD is both underdiagnosed and misdiagnosed. A third of those diagnosed with COPD on spirometry are not on inhaled therapies, suggesting that some will miss out on evidence-based treatment in the absence of this simple diagnostic modality. An Australian study in general practice found that 20% of those being treated for COPD did not meet the criteria once spirometry was performed. The majority of diagnoses of COPD can therefore be made in primary care if accurate spirometry is available without the need for further respiratory specialist input.

Several conditions are known to be underdiagnosed in patients with SMI as symptoms of organic disease are frequently misattributed to mental illness. Sleep disordered breathing (SDB) is known to occur in a higher prevalence in those with SMI. Drugs used in SMI may worsen sleep disorders, such as restless legs syndrome, obstructive sleep apnoea (OSA) and rapid eye movement (REM) disordered breathing.

The diagnosis of OSA requires overnight polysomnography (PSG). Patients likely to have a positive PSG can be predicted with clinical scoring systems, which include neck circumference, hypertension, loud snoring, history of witnessed apnoeas and body mass index. These scoring systems (i.e. OSA-50) have not been validated in the mental health population despite SMI being a risk factor for SDB. Establishing the prevalence of symptoms associated with SDB would aid in the identification and referral of patients with SMI to dedicated sleep units.

Our primary aim was to develop screening for common respiratory conditions, including COPD and symptoms associated with OSA in inpatients with SMI for which cost-effective and evidence-based interventions already exist. A secondary aim of this study was to assess the feasibility of employing a mental health nurse trained in spirometry to perform spirometry accurately in inpatients in order to obtain a diagnosis of COPD.

**Methods**

This was a cross-sectional study to describe the prevalence of respiratory illness, tobacco use and a range of physical health markers among a cohort of patients admitted to a major, urban mental health service over a 3-month period.

All patients aged 18 years and over admitted to The Prince Charles Hospital mental health unit were eligible for inclusion in this study provided written informed consent was given. Recruitment was limited by the availability of a study nurse with dedicated time of 1 day a week. A convenience sample was taken based on the availability of the study nurse to obtain consent and conduct interviews. Patients who were not inpatients on the day of nurse availability were therefore not eligible to be included in the study.

As part of routine clinical procedures, all patients admitted to the mental health service receive a medical review within 24 h by the resident medical officers. The eligible participants received a physical assessment with the addition of spirometry and a questionnaire (Supporting Information Appendix S1) to collect information regarding physical health indices. The full assessment questionnaire was a combination of standardised assessment questions utilising the Physical Health Check. Fagerström smoking inventory and predictors of OSA. Questions were asked to determine who was managing previously diagnosed conditions, such as diabetes or COPD, and whether current models of care were meeting the health needs of those with mental illness.

The questionnaire was completed by a healthcare professional in an interview format with the patient during their admission. Abnormal results, symptoms of respiratory or cardiac disease or evidence of chronic disease were managed either through referral to an inpatient specialty unit or follow up with a general practitioner (GP) as per the discretion of the treating psychiatry team. The frequency or outcome of such referrals was not recorded for the purposes of this study.

All patients were asked screening questions relating to the presence of common respiratory symptoms, such as cough and shortness of breath (Table 1).

Spirometry was performed with an EasyOne™ world-spirometer manufactured by Niche Medical. Patients over the age of 35 with a smoking history or respiratory symptoms received spirometry as guided by recommendations from the Australian Lung Foundation Australia. In addition, it was performed on all those over the age of 35 with symptoms of airway disease (e.g. dyspnoea, sputum production) as suggested by an online eight-question survey by the Lung Foundation Australia. The presence of a post-bronchodilator forced expiratory volume in 1 s/ forced vital capacity (FEV1/FVC) < 0.70 is considered consistent with COPD as defined by the Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria. Patients did not receive pre-spirometry bronchodilators. Spirometry was performed by a mental health nurse trained and credentialled in spirometry.

**Statistical methods**

Questionnaire responses were compiled and cross-checked for consistency. Categorical variables were described using frequencies and percentages, and summary statistics were derived for continuous variables. Independent sample t-tests were used to compare the mean values for spirometry.
variables across groups defined by tobacco use and age category. Associations between variables of interest and COPD and tobacco use were analysed by performing Chi-squared analysis or by using Fisher’s exact test when there were fewer than five observations in more than 20% of cells. The Stata statistical software package (StataCorp version 13) was used for all analyses.

### Ethics

Ethics approval for the study was obtained from The Prince Charles Hospital Ethics Committee.

### Results

Over the 3-month period of the study, 82 patients had sufficient data collected for inclusion in the final analysis. This represented approximately 25% of the inpatient population based on an average of 90 admissions per month. In the patients, 20% (17 patients) did not have a regular GP, and the majority (58%) attended more than one general practice.

Baseline characteristics, questionnaire responses and spirometry classification for the study participants are presented in Table 1. Of the 82 patients, 42 (51%) were male, and 46 (56%) had an SMI diagnosis of psychosis. Self-reported diagnoses revealed a high prevalence of medical conditions and symptoms. Of patients responding to the questionnaire, 18 (24%) self-reported a diagnosis of hypertension, 32 (41%) reported chest pain within the last 12 months, 21 (26%) self-reported a diagnosis of asthma, and 33 (44%) reported breathlessness (Table 1). Self-reported prevalence of substance use was high, with 41 (52%) reporting current tobacco use and 11 (14%) reporting regular cannabis use.

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</table>

BMI, body mass index; FEV1, forced expiratory volume in 1s; FVC, forced vital capacity; IQR, interquartile range.
A productive cough was reported by 30 (37%) of respondents, and this varied significantly with tobacco use, with sputum production reported by 53% of smokers compared to 22% of non-smokers ($P = 0.005$).

Of 57 patients, 10 (18%) with spirometry measures (Table 1) were classified as having COPD (FEV1/FVC ratio $< 0.7$). Of 80 patients, 6 self-reported a diagnosis of COPD. Of these, four had consistent spirometry results, one did not have results, and one had a borderline FEV1/FVC ratio of 0.7. Meanwhile, six patients with a FEV1/FVC ratio $< 0.7$ reported they had not been diagnosed with COPD. The available spirometry readings suggest that the self-reported diagnosis of COPD by subjects was correct.

Smokers were significantly more likely to have a productive cough than non-smokers. There were no other differences in the prevalence of other symptoms between smokers and non-smokers.

Symptoms associated with SDB, although non-specific, were prevalent in this cohort (Table 1). The majority of subjects (76%) woke feeling tired. Eight patients (11%) reported a diagnosis of OSA. Nine patients (13%) reported witnessed apnoeic episodes, which is associated with OSA.

**Discussion**

This cohort study revealed high rates of symptoms known to be associated with respiratory disease and SDB in an inpatient population in a mental health unit. Although many of these symptoms are not specific for respiratory disease, their presence would normally mandate further investigation by the patients’ GP. Although we demonstrated an association between smoking and reported productive cough, the study may have been underpowered to detect an association between smoking and other symptoms, such as wheezing. Symptoms such as chest pain are non-specific and may reflect a variety of pathologies, including ischaemic heart disease, COPD, biliary and gastric disease as well as functional disorders. Regardless of the eventual diagnosis, they would always warrant further investigation.

We were able to demonstrate a high rate of undiagnosed COPD and symptoms of airway disease in a population known to be at risk of premature death and morbidity.

Although we used spirometry with FEV1 as a biomarker for smoking-related airway disease, there is emerging evidence that smokers with symptoms of cough, wheezing, etc. have significant abnormality on CT chest scans without a change in FEV1. Therefore, solely relying on spirometry is likely to underestimate the extent of smoking-related lung disease particularly in a younger population. The mean age of the study cohort was 38 years, and it is likely that the end organ complications of risk factors such as smoking and obesity were not yet manifest. It is uncommon for spirometric confirmation of COPD to be present in even heavy smokers less than 40 years of age even if symptoms of smoking-related lung disease (e.g. chronic bronchitis) are present. It is possible that a similar study performed in an older group of patients with SMI in a community setting may have revealed even higher rates of COPD.

Consistent with other studies, patients with SMI had a higher rate of tobacco use than the general population. Currently, approximately 15% of the Australian population are smokers compared with 53% of the study cohort; 13% used cannabis at least monthly.

Smoking was associated with increased reported sputum production, which is consistent with smoking-related chronic bronchitis and is an early indicator of permanent lung damage.

An aim of this project was to determine the feasibility of a mental health nurse being trained in spirometry so as to expedite the diagnosis of COPD. In preparation for this study, a psychiatric nurse received formal training in spirometry. Although the spirometry performed during the study was not independently confirmed by a respiratory scientist, several internal controls suggest that measurements were accurate. The natural decline in FEV1 with age was confirmed with subjects over the age of 40 years having a lower FEV1 (Table 3). An important limitation of diagnosing COPD in this study was that prespirometry bronchodilators were not given by the study nurse. In order to differentiate COPD from asthma, a diagnosis of COPD requires a post-bronchodilator FEV1/FVC of $< 0.7$. At the time of this study, administration of salbutamol was not allowed in our hospital without a prescription.

**Table 3** Comparison of spirometry measures across categories defined by tobacco use and age

<table>
<thead>
<tr>
<th>Spirometry measure</th>
<th>Tobacco use = yes</th>
<th>Tobacco use = no</th>
<th>n†</th>
<th>Mean</th>
<th>SD</th>
<th>n†</th>
<th>Mean</th>
<th>SD</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>31</td>
<td>3.09</td>
<td>24</td>
<td>2.92</td>
<td>0.21</td>
<td>27</td>
<td>2.77</td>
<td>0.22</td>
<td>0.550</td>
</tr>
<tr>
<td>FEV1 (%predicted)</td>
<td>31</td>
<td>89</td>
<td>23</td>
<td>87</td>
<td>23</td>
<td>87</td>
<td>23</td>
<td>0.828</td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>31</td>
<td>3.92</td>
<td>24</td>
<td>3.65</td>
<td>0.28</td>
<td>27</td>
<td>3.36</td>
<td>0.23</td>
<td>0.418</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>31</td>
<td>0.78</td>
<td>24</td>
<td>0.81</td>
<td>0.02</td>
<td>27</td>
<td>0.77</td>
<td>0.03</td>
<td>0.273</td>
</tr>
</tbody>
</table>

†One patient did not have a recorded FEV1 (%predicted) despite having an FEV1 measured. FEV1, forced expiratory volume in 1s; FVC, forced vital capacity.
medical prescription. Therefore, for a formal diagnosis of COPD to be made, participants would require further post-bronchodilator spirometry. It is possible that some patients may have not fulfilled the criteria for COPD with post-bronchodilator spirometry.

The diagnosis of asthma requires the demonstration of reversibility of airflow obstruction with the administration of salbutamol. For this diagnostic method to be accurate, an asthmatic’s usual inhalers need to be withheld before testing. As this requires forward planning, this was not pursued in this study given we were performing opportunistic ‘spot’ testing of patients in the mental health ward. Nevertheless, the clarification or exclusion of a diagnosis of asthma in those with suggestive symptoms is clearly important and should be a focus of future studies.

Barriers to the accurate diagnosis of COPD include lack of availability of spirometry. We believe this is the first study to show that it was feasible for a mental health nurse to perform spirometry independently in this population and detect previously undiagnosed COPD. This opportunistic testing for a common and treatable condition could lead to improved quality of life for many people with SMI once appropriate therapies have been initiated. There is strong evidence that treatment of COPD with inhaled therapies, pulmonary rehabilitation, vaccination, and smoking cessation prevents mortality and morbidity. These interventions are cost effective and within the capacity of primary care to provide.

The majority of patients reported feeling tired during the day. This is a common symptom and not specific for SDB; however, nine (13%) reported witnessed apnoeic episodes, which is a more sensitive marker of OSA. The symptoms of SDB in SMI are non-specific, and its interaction with centrally acting drugs, such as those used in mental illness, are complex. A formal diagnosis therefore requires PSG, and clinical pathways are required to identify those with SMI likely to benefit from diagnosis and treatment.

Vaccination rates for influenza and pneumococcus were low. The current Australian guidelines suggest all smokers be vaccinated with the 23 valent polyvalent pneumococcal vaccine at least once. Given that only two patients could recall being vaccinated for pneumococcus, this suggests a gap in preventative care that could be easily addressed. Vaccination rates for influenza were low. Australian guidelines for annual influenza vaccine include those with severe asthma and COPD.

Limitations of this study include that it relied heavily on patient recall of past medical diagnoses and interventions (such as vaccination), which may not have been accurate, particularly in the setting of an acute psychiatric crisis. As many of these symptoms are non-specific, we do not know whether time and resources spent on investigating them would have ultimately led to a beneficial change in management. The study population was young, with a median age of 36 years. It is possible that focusing on some aspects of screening in an older group would have yielded higher rates of certain symptoms, such as those associated with cardiac disease. It is likely that recruitment would have been increased by greater study nurse availability and a shortened questionnaire that was time intensive and that contained domains which were of low yield.

As we were unable to recruit the majority of inpatients over the study period, we cannot be certain that we have captured a representative sample of the inpatient mental health population. As we only enrolled inpatients, we cannot generalise these findings to the broader population, including those in the outpatient setting.

For a comprehensive programme of preventative medicine and enhanced diagnosis of medical comorbidity to be implemented in the mental health population, dedicated medical and nursing staff is likely to be required. The ideal person to manage these issues is the patient’s GP, and indeed, many of these patients will already have chronic disease plans in place as well as regular GP reviews. However, the high proportion of patients accessing multiple general practices and without a regular GP raises concerns over the fragmentation of care. Relying solely on primary care providers may therefore miss opportunities for diagnosis in this group. It is important to construct an integrated care model involving hospital-and community-based mental health teams, GP and other speciality units as appropriate. Different models should be explored, including having chronic disease nurses embedded within mental health units liaising directly with GP or, alternatively, GP working within psychiatry units.

Conclusion

This pilot study identified a high rate of respiratory symptoms and spirometry consistent with COPD in a relatively young patient population with SMI. We were able to demonstrate that it was feasible for mental health nurses to perform spirometry in the context of an acute psychiatric admission without the need for referral to a respiratory investigation unit.

There was a high rate of symptoms, such as fatigue, and reports of witnessed apnoeic events while sleeping, which – although non-specific – are associated with SDB as well as other treatable conditions, such as heart failure. Tobacco use was high and consistent with
previously published reports, supporting the emphasis on tobacco smoking strategies in mental health units. This study demonstrates that the high levels of physical comorbidity identified in inpatients with SMI warrant an expansion of resources dedicated to the diagnosis and treatment of common chronic diseases. For such a programme to be cost effective, it would need to be patient centred and integrated with primary care to avoid duplication of efforts. It would also require enhanced communication between all levels of healthcare providers.

References

1 Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. BMJ 2013; 346: 12539.


Supporting Information

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

Appendix S1. The Prince Charles Hospital mental and physical health questionnaire.
Characterisation of clonal Philadelphia-negative cytogenetic abnormalities in a large cohort of chronic myeloid leukaemia

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Key words
chronic myelogenous leukaemia, tyrosine kinase inhibitor, clonal Philadelphia chromosome-negative cytogenetic abnormality.

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Abstract

Background: Clonal Philadelphia (Ph)-negative cytogenetic abnormalities (CPCA) have been reported in chronic myeloid leukaemia (CML) patients treated with either interferon or tyrosine kinase inhibitor (TKI). However, the incidences and types of these cytogenetic abnormalities after treatment vary due to the limited populations enrolled.

Methods: We analysed the frequency and types of CPCA in a cohort of 607 CML patients in the chronic phase after TKI treatment. We also followed up these CPCA with a median of 31.8 months (range from 11 to 63 months) from diagnosis and investigated their effects on disease progression.

Results: We found 18 out of 607 CML patients had cytogenetic abnormality in the Ph-negative cells with an incidence of 3%. In total, six types of chromosomal abnormalities have been identified in these 18 patients with the majority of them aneuploidy abnormalities, especially the trisomy 8. Four of 18 patients (22.2%) were noted to have several abnormalities in the Ph-negative cells. Furthermore, follow-up studies of these CPCA showed that they could be either persistent or transient (15 vs 3 patients), and may not affect disease progression since none of them developed transformed myelodysplasia or transformed acute myeloid leukaemia.

Conclusion: Three percent of CML patients in the chronic phase were observed to have CPCA during TKI treatment. Our results suggest that the detection of CPCA in CML may not predict disease progression.

Introduction

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disorder characterised by the presence of the Philadelphia (Ph) chromosome, which derives from a reciprocal translocation between chromosome 9 and chromosome 22. The resulting chromosomal rearrangement generates the BCR/ABL1 fusion gene, which encodes a novel oncogenic protein BCR/ABL.1 The BCR/ABL protein contains a constitutive tyrosine kinase domain from the ABL fusion partner, which plays an essential role in the leukaemogenesis of CML. For CML treatment, the conventional cytostatic agents, such as hydroxyurea, busulfan, interferon (IFN) or haemopoietic stem cell transplantation were the choices for the management of CML patients. In more recent decades, targeting of the kinase activity of BCR/ABL with small-molecule inhibitors, mainly the tyrosine kinase inhibitor (TKI) imatinib mesylate and several more recently introduced agents, have been clinically proven to be effective in the front-line management of CML.

Interestingly, during treatment with TKI, a small percentage of CML patients have been reported to carry clonal cytogenetic abnormalities in the clonal Ph-negative cytogenetic abnormalities (CPCA), including trisomy 8, chromosome 7 defects and nullisomy Y. However, due to the limited size of the populations involved, the rates of CPCA vary greatly in the literature from 2 to 15%.2–5 The mechanism for CPCA is still unknown. Although the TKI and their intermediates are genotoxic at high concentration in vitro,6–8 some data reported that this phenomenon was not caused by TKI treatment because CPCA could be found in Ph-negative cells prior to TKI treatment.8,9

CPCA as a phenomenon after TKI treatment in a subset of CML patients have had no obvious effects on
disease progression. However, chromosomal abnormalities, such as trisomy 8 and chromosome 7 defects, were also reported in other haematologic malignancies, including myelodysplastic syndromes and acute myeloid leukaemia. Therefore, the mechanism and clinical significance of CPCA in CML still needs to be elucidated.

In this study, we conducted a systematic study of CPCA with a large cohort of 607 CML patients in chronic phase. We found that the incidence of CPCA in CML was 3% with the majority of them being trisomy 8 and characterised six different types of CPCA. Furthermore, we also followed up these patients with CPCA with a median of 31.8 months (range: 11–63 months) from diagnosis and found that these patients respond well to TKI treatment, which suggested that CPCA might have no obvious effects on disease progression.

Methods

Patient enrolment

Medical records of all consecutive CML patients in our institution from 2009 to 2013 were reviewed to identify patients with chromosomal abnormalities in Ph-negative metaphases during imatinib treatment. Altogether, 607 consecutive CML patients (384 males and 223 females, median age: 47 years; range: 13–86 years) were enrolled in this study. The diagnosis of CML was based on cytogenetic and/or TaqMan-probe-based reverse transcription quantitative polymerase chain reaction (RT-qPCR) analysis. Most of the patients received TKI mostly imatinib mesylate, either as the first-line therapy or after interferon failure. This study was approved by the Research Ethics Committee at the Union Hospital.

Cytogenetic analysis

Conventional cytogenetic studies were performed on 2–4 mL of bone marrow or peripheral blood. Two cultures from each patient were initiated in complete tissue culture medium. The cells were incubated for 8–12 h without mitogen. Representative G-bands by trypsin using Leishman’s stain banding was carried out and 20 metaphase cells of each patient were analysed. If less than 20 metaphase cells available, the number of metaphase cells analysed in the study had been indicated in the Results section. Clonal chromosome aberrancies were defined as two or more cells showing the same chromosomal gain or structural abnormality, or three or more cells with the same chromosomal loss. Cytogenetic analysis was performed according to the Human System for Cytogenetic Nomenclature 2009. The cytogenetic response was classified based on the percentage of Ph-positive (Ph+) cells in metaphase as follows: complete cytogenetic response, 0%; partial cytogenetic response, 1–35%; minor cytogenetic response, 36–65%; minimal cytogenetic response, 66–95%; no cytogenetic response, 96–100% Ph+ cells.10

Fluorescence in situ hybridisation analysis

To confirm the cytogenetic results, fluorescence in situ hybridisation (FISH) analysis was performed with the commercially available FISH probes, including t(9;22) and chromosome 8 FISH probes (Abott, Chicago, IL, USA). The slides used for FISH studies were the same as cytogenetic analysis. The hybridisation was done in a Vysis Hybridiser (Abott) according to the manufacturer’s protocol. We used the denaturation temperature of 58°C. A total of 400 interphase cells was scored for each probe with a FISH analysis software.

TaqMan-probe-based RT-qPCR

For the molecular biological analyses, total mRNA was isolated with trizol with the same specimen as used for the cytogenetic analysis. The BCR/ABL1 transcripts were detected with the StepOne Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). The PCR primers and TaqMan probes for BCR/ABL1 were used according to the published method.11 The RT-qPCR results were also normalised with a conversion factor IS (International harmonisation of scale) in accordance with the international standard.

Follow up and response assessment

Follow up and response assessment were scheduled with cytogenetic analysis for every 3 months in the first year, then every 6 months for the next 2–3 years, then as clinically indicated. Molecular response was generally assessed every 3 months in the first year, and then every 6 months after the first year. The response assessment for each CML patient was performed based on the cytogenetic and molecular analysis every 3 months for the first 12 months, and then every 6 months afterward.

Results

Characterisation of the CPCA in a cohort of 607 CML patients

We characterised a cohort of 607 CML patients in our centre from 2009 to 2013 and identified CPCA during TKI therapy. These CML patients contain 384 males and 233 females with a median age of 47 years (range:
13–86 years). From these 607 CML patients, we detected CPCA from 18 CML patients (15 males and 3 females; 3.0%) during TKI treatment with a median follow up of 31.8 months (range: 11–63) from diagnosis. In total, six types of chromosomal abnormalities were identified in these 18 patients. The period between the detection of CPCA from these patients and the usage of TKI ranged from 3 to 20 months with a median of 11.2 months. The profiles of cytogenetic abnormalities of the 18 patients are summarised in Table 1.

Analysis of these CPCA revealed that most of these patients carried aneuploid abnormalities especially gain of chromosome 8 (17/18, 94.4%), which was consistent with the previous report of CPCA in a subset of CML patients after TKI treatment.2–5 Besides, defects of chromosome 7, including the loss of the entire or part of chromosome 7, were the second most frequent abnormalities (4/18; 22.2%) CML patients were identified to have the −7/7q− abnormalities (Table 1, patients 7, 10, 14 and 18), which was also consistent with previous studies of chromosome 7 defects in CML patients.2–5 Y chromosome abnormalities were also identified in four patients (patients 9, 14, 16 and 18; 4/18, 22%). Interestingly, we also identified some new abnormalities, including chromosome 2, chromosome 6 and two unidentified chromosomes (patients 14 and 18). Furthermore, we did not detect any structural chromosome changes in karyotyping analyses except chromosome number changes.

**Pattern of CPCA in CML patients during TKI treatment**

As mentioned above, trisomy 8 was the most abundant abnormality in CPCA and was detected in 17 out of 18 patients. Interestingly, in our study, we also found 4 out of 18 patients (22.2%) carrying several abnormalities in Ph-negative metaphase cells: patient 14 carried −7, +8, −Y, +Y and +mar in one examination; patient 18 had Ph+ clones as well as four types of CPCA. Interestingly, it changed in two patients (patients 7 and 9). Patient 7 had trisomy 7 besides persistence of +8 after 4 months. Patient 9 gained +Y afterwards and trisomy 8 disappeared after a period of 45 months.

Follow-up studies were performed to monitor CPCA from these 18 patients and we found that these abnormalities could be either persistent or transient (15 and 3 patients respectively) as shown in Figure 1. In most of the patients (83%), the abnormalities persisted during TKI treatment and could be detected until the end-point of this study. However, three patients (patients 9, 10 and

**Table 1** Cytogenetic abnormalities present in 18 patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex</th>
<th>Age</th>
<th>Cytogenetic</th>
<th>Time with TKI (months)</th>
<th>Time from diagnosis (months)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>35</td>
<td>47,XX,+8[6]/46,XX[14]</td>
<td>13</td>
<td>27</td>
<td>CP</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>50</td>
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<td>NA</td>
<td>NA</td>
<td>CP</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>34</td>
<td>47,XX,+8[10]/46,XX[10]</td>
<td>NA</td>
<td>NA</td>
<td>CP</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>34</td>
<td>46,XX,+8[17]/46,XX[10];9;22 (1)/q34;q11[3]</td>
<td>13</td>
<td>17</td>
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<td>6</td>
<td>M</td>
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<td>NA</td>
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<td>9</td>
<td>13</td>
<td>CP</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>44</td>
<td>47,XY,+8[4]/46,XY[9,22]/q34;q11[1][2]/46,XY[10]</td>
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<td>20</td>
<td>46,XY,del([7][q31.2]/[5])/46,XY[15]</td>
<td>20</td>
<td>20</td>
<td>CP</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>44</td>
<td>47,XY,+8[19]/46,XY[10,22]/q34;q11[1]</td>
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<td>22</td>
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<tr>
<td>18</td>
<td>M</td>
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<td>47,XY,+8[7]/45,XY,−Y,+7,+mar[6]/46,XY[9,22]/q34;q11[1]</td>
<td>19</td>
<td>36</td>
<td>CP</td>
</tr>
</tbody>
</table>

CP, chronic phase; NA, not available; TKI, tyrosine kinase inhibitor.
had a different pattern than persisting and the CPCA abnormalities from these patients were transient during TKI treatment. In addition, the abnormalities seen in patient 9 (1/18) occurred and disappeared twice. These data suggested that some patients might have a dynamic change of CPCA during TKI therapy.

Most of the patients had a high abundance of CPCA in the metaphase cells as shown in Figure 1. In 11 (11/18, 61.1%) patients, the metaphase cells with CPCA were greater than 50% of the cells analysed. Interestingly, we also observed +8 in both Ph-positive and Ph-negative metaphase cells from patient 12 at the diagnosis stage. This phenomenon was very rare and the clinical significance of this event still needed further effects to study.

CPCA does not predict the TKI response and disease progression

Since CPCA only could be detected in a subset of CML patients after TKI therapy, we followed up TKI response and disease progression in these patients. We found that 17 (17/18, 94.4%) of the patients achieved major cytogenetic response (MCyR) in a median of 15.0 months (7.0–34.0) and maintained it for a median of 16.0 months (1.0–50.0). Although patient 11 relapsed during imatinib mesylate treatment, this patient achieved MCyR again after the treatment with dasatinib. Though the RT-qPCR result of patient 11 suggested that he might aggravate in acceleration phase (AP), the emergence of CPCA at the time when he had an apparent molecular response that the BCR/ABL1 transcript was at a very low level. Moreover, this patient did not achieve MCyR or major molecular response (MMR) after the use of imatinib for 6 months. He achieved MCyR after treatment with dasatinib and then exhibited trisomy 8 in Ph− cells. The Ph+ cells of this patient varied at times, but the isolated +8 cells persisted. Finally, he achieved both MCyR and MMR with continuing treatment with dasatinib.

All of the 18 patients eventually fulfilled the criteria for MMR with complete molecular response in six patients (6/18, 33.3%) using high-sensitive RT-qPCR. Only patient 16 failed to achieve MCyR, but he did achieve MMR. All of the patients were still alive at the end of this study. Overall, these 18 patients did not show any evidence of TKI resistance.

Discussion

CML is a clonal myeloproliferative disorder characterised by the presence of the Ph chromosome. The occurrence of CPCA in CML patients after TKI therapy varies greatly in published literature. According to published studies, the incidence of CPCA is between 2 and 15% during the management of CML. In our study, we enrolled a large cohort of 607 CML patients from our centre and followed them for a median of 31.8 months. We found that the occurrence of CPCA was 3.0%, consistent with previous reports. Karyotyping analysis also revealed a total of six numerical chromosome abnormalities, involving chromosomes 7, 8 and Y. We also identified chromosome 6, and two unidentified chromosomal abnormalities in this large set of patients. Consistent with previous
reports, trisomy 8 was the most common abnormality followed by deletion of whole or part of chromosome 7. We also found that trisomy 8 existed in both of Ph+ and Ph− cells (patient 12).

The mechanism of CPCA occurrence after TKI treatment is still not clear. With the excellent therapeutic effect of TKI therapy, long-term survival of CML patients has dramatically improved resulting in a large number of surviving CML patients. Some of these patients may have coexisting myelodysplastic syndromes or other types of leukaemia. Although trisomy 8 and chromosome 7 defects are observed in many other haematologic malignancies, such as myelodysplastic syndromes and acute myeloid leukaemia,13–17 here, we did not observe the occurrence of either of these conditions.

CPCA is different from clonal evolution, which is the acquisition of additional karyotype abnormalities in Ph-positive cells. Clone evolution, characterised by several non-random chromosome aberrancies,18,19 is one of the major mechanisms for disease progression and TKI resistance in CML.19 Generally, clonal evolution predicts deterioration of disease and is associated with a poor prognosis. Distinguished from clonal evolution, CPCA is mostly discovered in patients still in chronic phase, especially in patients who have achieved MCyR or MMR. In this study, we found that the overall prognosis for patients with CPCA was similar to that for other patients who achieved an MCR.3,20 No evidence for disease progression was observed in our patients, even though no changes were made to treatment. For the 18 patients followed up for 31.8 months (range 11–63 months) from diagnosis the outcome was excellent. At the time of this report, all of the patients were alive in continuing chronic phase. These results were consistent with several other earlier reports.4,15 Nevertheless, because of the heterogeneous clinical characteristics of CPCA, the final outcomes might not yet have been realised. We cannot exclude the possibility that some patients with CPCA might have an increased risk of myelodysplasia or acute myeloid leukaemia given a much longer follow-up period.21

## Conclusion

CPCA clones perhaps derive from residual non-leukaemic haemopoietic stem cells22 in that the high selectivity of TKI eradicating Ph+ cells may harbour and uncover these clones. However, the detailed mechanism for CPCA still needs further investigation. In summary, we conducted a systematic review of CPCA in a large cohort of CML patients and studied the incidence and potential effects of CPCA on TKI response and disease progression. This study provides information about CPCA and brings insight into this phenomenon in CML patients after TKI therapy.

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Urolithiasis is associated with an increased risk of stroke: a population-based 5-year follow-up study

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Key words
cerebrovascular disease, intracerebral haemorrhage, ischaemic stroke, National Health Insurance Research Database, urolithiasis.

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Abstract
Background: Epidemiological studies have reported an association between urolithiasis and cardiovascular disease. However, studies examining the risks of ischaemic and haemorrhagic stroke in patients with urolithiasis are limited.

Aims and methods: By using a nationwide population database, we conducted a matched cohort study to investigate the association between urolithiasis and longitudinal risks of ischaemic and haemorrhagic stroke.

Results: The urolithiasis and non-urolithiasis cohorts included 12 979 and 64 895 patients respectively. Of these, 728 (5.6%) and 2802 (4.3%) patients in the urolithiasis and non-urolithiasis cohorts, respectively, had a stroke during the 5-year follow-up period. The hazard ratio (HR) for stroke was 1.19 times higher (95% confidence interval [CI] = 1.10–1.29; P < 0.001) in the urolithiasis cohort than in the non-urolithiasis cohort after adjustment for potential confounders. The risk of both ischaemic (adjusted HR = 1.16; 95% CI = 1.05–1.29) and haemorrhagic stroke (adjusted HR = 1.30; 95% CI = 1.03–1.64) remained significant in the urolithiasis cohort. Furthermore, the risk of stroke was significant in both men (adjusted HR = 1.16; 95% CI = 1.05–1.28) and women (adjusted HR = 1.26; 95% CI = 1.10–1.45). Middle-aged (40–59 years; adjusted HR = 1.26; 95% CI = 1.10–1.45) and older (≥60 years; adjusted HR = 1.14; 95% CI = 1.03–1.27) patients had a particularly high risk of stroke.

Conclusions: The present study detected an increased risk of both ischaemic and haemorrhagic stroke in patients with urolithiasis, particularly in those older than 40 years.

Introduction
Stroke remains a leading public health concern. The numbers of events and deaths due to stroke continue to increase globally. Stroke is also currently the third largest contributor to disability in developed countries. This emphasises the need for identifying populations at a high risk of stroke and developing efficient stroke prevention strategies.

Urolithiasis is a common genitourinary disease. The prevalence and incidence of urolithiasis are reported to be increasing worldwide. Similar to cardiovascular diseases, urolithiasis has a higher incidence in men. In addition, epidemiological studies have reported an association between urolithiasis and hypertension, diabetes mellitus, metabolic syndrome and subclinical carotid atherosclerosis, all known risk factors for cardiovascular disease. Evidence of an association between urolithiasis and cardiovascular risk factors suggests that urolithiasis is both a chronic and systemic disease representing the interaction of multiple vascular risk factors.

Although the cause–effect relationship is unclear, several studies have reported that patients with urolithiasis may have an increased risk of myocardial infarction and cardiovascular diseases. This evidence suggests that urolithiasis is not only a genitourinary disease but also a potential risk factor or indicator of future cardiovascular events. Previous studies have demonstrated an increased risk of stroke in patients with urolithiasis. However, studies separately examining the risks of ischaemic and haemorrhagic stroke are limited. In addition, evidence regarding the age and gender effects of urolithiasis on the risk of stroke is still inconclusive. Therefore, by using a nationwide population database, we conducted a matched
cohort study to investigate the association between urolithiasis and a longitudinal risk of ischaemic and haemorrhagic stroke stratified by age and gender.

Methods

Data source

This retrospective cohort study was conducted using claims data from the National Health Insurance Research Database (NHIRD), Taiwan. The National Health Insurance (NHI) programme, which was implemented on 1 March 1995, has reimbursed the healthcare costs of 99.9% of Taiwan’s population as of 2014. The NHIRD, based on the NHI programme and managed by Taiwan’s National Health Research Institutes (NHRI), provides comprehensive healthcare information regarding the insured.

In the present study, data were obtained from the Longitudinal Health Insurance Database (LHID) 2005, a subset of the NHIRD. The LHID2005 data set contains the historical healthcare data of 1 million randomly sampled beneficiaries who enrolled in the NHI programme in 2005. The LHID2005 database enables researchers to trace the medical service utilisation of these beneficiaries. The NHRI claims that no statistically significant differences exist in the age, gender, geographical region and healthcare cost data between the LHID2005 and all claims.

This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital, Taiwan. All personal identification information is encrypted before being released to the public to protect patient privacy. Therefore, the review board waived the requirement of obtaining written informed consent from the study’s participants.

Participants

We retrospectively examined urolithiasis and matched non-urolithiasis cohorts to investigate the relationship between urolithiasis and the risk of stroke. The urolithiasis cohort included patients aged ≥20 years and who were diagnosed with urolithiasis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 592.0, 592.1, 594.0 and 594.1) between 1 January 2001, and 31 December 2005, during one inpatient or two outpatient care visits. The diagnosis of urolithiasis had to have been made by an urologist, nephrologist or internist. Patients with a history of urolithiasis before 1 January 2001 were excluded from the present study. The date of initial urolithiasis diagnosis for each study patient was considered to be the index date.

The matched non-urolithiasis cohort comprised non-urolithiasis patients who were matched to each patient with urolithiasis – in a ratio of 5:1 – based on age, gender and index year and randomly selected from the remaining population in the same database. Patients with a history of stroke (ICD-9-CM 430–438) before enrolment were excluded from both the urolithiasis and non-urolithiasis cohorts. The study patients were individually followed up for 5 years from their index date to evaluate the occurrence of stroke.

Main outcome measures

The outcome of interest was defined as a receipt of stroke diagnosis after the index date. Stroke diagnosis (ICD-9-CM 430–438) was defined as the receipt of outpatient care twice or inpatient care once for stroke and diagnosis by a neurologist, neurosurgeon or cardiovascular specialist. Haemorrhagic stroke (ICD-9-CM 430–432) and ischaemic stroke (ICD-9-CM 433–435) were recorded separately.

We identified several comorbidities before the index date as potential confounding factors for stroke: hypertension (ICD-9-CM 401–405), diabetes mellitus (ICD-9-CM 250) and hyperlipidaemia (ICD-9-CM 272). All comorbidities were diagnosed by physicians during two outpatient visits or one inpatient visit.

Statistical analyses

A Pearson Chi-squared test was performed to evaluate differences in the categorical variables – including urbanisation level, monthly income, geographical region and comorbidities – between the urolithiasis and non-urolithiasis cohorts. The Kaplan–Meier survival test was performed to estimate stroke-free survival rates in the urolithiasis and non-urolithiasis cohorts, and a log-rank test was used to analyse the differences between the survival curves. Cox proportional hazards regression analysis was performed to examine the crude and adjusted hazard ratios (HR) for total stroke, ischaemic stroke and haemorrhagic stroke in the urolithiasis cohort compared with the non-urolithiasis cohort during the 5-year follow-up period after adjustment for gender, age, urbanisation level, geographical region, monthly income, hypertension, hyperlipidaemia and diabetes mellitus.

Furthermore, age- and gender-stratified analyses were performed using the Cox proportional hazards regression model to evaluate the risk of stroke in the urolithiasis cohort across different age groups and genders. A two-sided \( P < 0.05 \) was considered statistically significant.
Results

The urolithiasis and non-urolithiasis cohorts included 12,979 and 64,895 patients respectively. The distributions of sociodemographic characteristics and the relative comorbidities of the urolithiasis and non-urolithiasis cohorts are presented in Table 1. Of the 77,874 patients, 68.4% were men and 31.8%, 46.9% and 21.3% belonged to the age groups 20–39, 40–59 and ≥60 years respectively. The urolithiasis cohort was more likely to reside in less urbanised communities and had a lower monthly income than the non-urolithiasis cohort. In addition, the urolithiasis cohort was more vulnerable to hypertension (47.5% vs 37.9%, \( P < 0.001 \)), hyperlipidaemia (41.3% vs 32.3%, \( P < 0.001 \)) and diabetes mellitus (26.6% vs 21.0%, \( P < 0.001 \)) than the non-urolithiasis cohort.

In total, 3,530 (4.5%) patients had a stroke during the 5-year follow-up period, of whom 728 (5.6%) and 2,802 (4.3%) were patients in the urolithiasis and non-urolithiasis cohorts respectively (Table 2). Cox proportional hazards regression analysis demonstrated that the crude HR for stroke was 1.32 times higher (95% confidence interval [CI] = 1.21–1.43; \( P < 0.001 \)) in the urolithiasis cohort than in the non-urolithiasis cohort. The risk of stroke remained significant after adjustment for the potential confounders: gender, age, urbanisation level, geographical region, monthly income, hypertension, hyperlipidaemia and diabetes mellitus (adjusted HR = 1.19; 95% CI = 1.10–1.29; \( P < 0.001 \)). Kaplan–Meier analysis demonstrated that the urolithiasis cohort had a significantly lower 5-year stroke-free survival rate than the non-urolithiasis cohort (log-rank test, \( P < 0.001 \); Fig. 1).

We further analysed ischaemic and haemorrhagic stroke separately. Of the patients, 2,276 (2.9%) presented with ischaemic stroke and 419 (0.5%) with haemorrhagic stroke during the 5-year follow-up period (Table 2). Cox proportional hazards regression analysis demonstrated that the crude HR for ischaemic stroke was 1.31 times higher (95% CI = 1.18–1.45; \( P < 0.001 \)) in the urolithiasis cohort than in the non-urolithiasis cohort. For haemorrhagic stroke, the crude HR was 1.43 times higher (95% CI = 1.14–1.80; \( P < 0.01 \)) in the urolithiasis cohort than in the non-urolithiasis cohort. The risk of

### Table 1: Demographic characteristics of the selected patients, stratified by the presence and absence of urolithiasis (n = 77,874)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with urolithiasis (n = 12,979)</th>
<th>Patients without urolithiasis (n = 64,895)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8,881 (68.4%)</td>
<td>44,405 (68.4%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4,098 (31.6%)</td>
<td>20,490 (31.6%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–39</td>
<td>4,130 (31.8%)</td>
<td>20,650 (31.8%)</td>
<td></td>
</tr>
<tr>
<td>40–59</td>
<td>6,088 (46.9%)</td>
<td>30,440 (46.9%)</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>2,761 (21.3%)</td>
<td>13,805 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>Follow-up, mean (SD) (years)</td>
<td>4.82 (0.82)</td>
<td>4.89 (0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urbanisation level</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 (most urbanised)</td>
<td>3,971 (30.6%)</td>
<td>22,080 (34.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>3,810 (29.4%)</td>
<td>18,201 (28.0%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2,218 (17.1%)</td>
<td>10,658 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>4 (least urbanised)</td>
<td>2,980 (23.0%)</td>
<td>13,956 (21.5%)</td>
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</tr>
<tr>
<td>Monthly income</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>2,159 (16.6%)</td>
<td>10,673 (16.4%)</td>
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</tr>
<tr>
<td>NT$1–15 840</td>
<td>1,779 (13.7%)</td>
<td>8,552 (13.2%)</td>
<td></td>
</tr>
<tr>
<td>NT$15 841–25 000</td>
<td>5,394 (41.6%)</td>
<td>26,573 (40.9%)</td>
<td></td>
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<tr>
<td>≥25 001</td>
<td>3,647 (28.1%)</td>
<td>19,097 (29.4%)</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>6,167 (47.5%)</td>
<td>24,597 (37.9%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6,812 (52.5%)</td>
<td>40,298 (62.1%)</td>
<td></td>
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<tr>
<td>Hyperlipidaemia</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Yes</td>
<td>5,354 (41.3%)</td>
<td>20,989 (32.3%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7,625 (58.7%)</td>
<td>43,906 (67.7%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>3,457 (26.6%)</td>
<td>13,601 (21.0%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9,522 (73.4%)</td>
<td>51,294 (79.0%)</td>
<td></td>
</tr>
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</table>
both ischaemic and haemorrhagic stroke remained significant after adjustment for potential confounders: gender, age, urbanisation level, monthly income, geographical region, hypertension, hyperlipidaemia and diabetes mellitus (adjusted HR = 1.16; 95% CI = 1.05–1.29; P < 0.01 for ischaemic stroke and adjusted HR = 1.30; 95% CI = 1.03–1.64; P < 0.05 for haemorrhagic stroke).

Table 3 presents the differences in the risk of stroke between the urolithiasis and non-urolithiasis cohorts after gender and age stratification. Compared with participants without urolithiasis, both men (adjusted HR = 1.16; 95% CI = 1.05–1.28; P < 0.01) and women (adjusted HR = 1.26; 95% CI = 1.10–1.45; P < 0.01) with urolithiasis had a significantly higher risk of stroke after adjustment for potential confounders.

In addition, age stratification demonstrated that middle age (40–59 years; adjusted HR = 1.26; 95% CI = 1.10–1.45; P < 0.01) and being elderly (≥60 years; adjusted HR = 1.14; 95% CI = 1.03–1.27; P < 0.05) in the urolithiasis cohort resulted in a significantly higher risk of stroke than in the non-urolithiasis cohort after adjustment for potential confounders. By contrast, the young age group (≤39 years) did not exhibit a significantly increased risk of stroke in the urolithiasis cohort compared with the non-urolithiasis cohort during the 5-year follow-up period (adjusted HR = 1.21, 95% CI = 0.82–1.77) (Table 3).

**Discussion**

The present study explored the association between urolithiasis and the risk of stroke using NHIRD data during a 5-year follow-up period. The principal finding was that after adjustment for possible confounders, the urolithiasis cohort exhibited a 1.19 times higher risk of stroke than the non-urolithiasis cohort within 5 years. The risk was significant in both men and women. Middle-aged (ages 40–59 years) and older (≥60 years) patients with urolithiasis had a particularly high risk of stroke.

The results are in agreement with longitudinal studies, which have reported an association between urolithiasis and increased risk of either type of stroke. Some studies have suggested that urolithiasis is only associated with an increased risk of ischaemic stroke, and the association between urolithiasis and haemorrhagic stroke
remains inconclusive. Therefore, we further examined the association between urolithiasis and stroke subtype. Our study demonstrated that the urolithiasis cohort had a 1.16 times and 1.30 times higher risk of ischaemic and haemorrhagic stroke than the non-urolithiasis cohort respectively. These findings agree with our hypothesis that patients with urolithiasis are at an increased longitudinal risk of both ischaemic and haemorrhagic stroke, particularly when older than 40 years.

The design of this study enabled the identification of a temporal association between urolithiasis and stroke. However, the causal relationship and pathophysiological mechanisms linking urolithiasis and stroke remain unclear. Several theories can be discussed. First, there is strong evidence that urolithiasis is associated with several systemic diseases, including metabolic syndrome, hypertension, diabetes mellitus, increased arterial stiffness and subclinical atherosclerosis. Our study also demonstrated that the urolithiasis cohort was more vulnerable to hypertension, hyperlipidaemia and diabetes mellitus. The relatively higher prevalence of these cardiovascular risk factors in patients with urolithiasis may contribute to the higher risk of both ischaemic and haemorrhagic stroke in this population. However, after adjustment for hypertension, hyperlipidaemia and diabetes mellitus, the risk of stroke remained higher in the urolithiasis cohort.

Second, urolithiasis and stroke share a common pathophysiological basis. Both clinical and experimental investigations have indicated that oxidative stress and systemic inflammation may be involved in the association between urolithiasis and stroke. Oxidative stress and systemic inflammation have been proposed to play a role in the formation of urolithiasis. Several inflammatory markers were found to be elevated in patients with urolithiasis. Moreover, patients with urolithiasis were discovered to have lower serum antioxidant levels. The overproduction of reactive oxygen species and alterations of the antioxidant system, which induce inflammation, are key pathophysiological markers of cardiovascular diseases. In addition, emerging evidence supports the novel concept that inflammation itself can induce oxidative stress during stroke. Therefore, an integrative concept describing a vicious cycle was developed to indicate the interconnection between oxidative stress and inflammation, which converges to both urolithiasis and stroke.

Third, evidence suggests that the process of primary stone formation in the renal papilla is similar to the evolution and progression of atherosclerotic plaques in arteries and capillaries in other parts of the body, which are known to contribute to stroke. Stoller et al. proposed a vascular theory describing the formation of urolithiasis in which the primary event of calcium nephrolithiasis may begin in a vascular injury at the tip of the renal papilla, resulting in calcification of the damaged vessel wall and then serving as a nidus for calculus formation. Such a process is analogous to atherosclerosis occurring elsewhere in the vascular system. Therefore, urolithiasis may present as an early process of atherosclerosis in cerebral vessels, which results in a future stroke.

The strengths of the present study include the use of a longitudinal population-based data set, which enabled us to trace all patients in both cohorts for the development of stroke during the study period. The data set also allowed us to exclude patients with a history of stroke before inclusion, a predictor for stroke. However, the results of the present study must be interpreted with caution because of the following limitations. First, the diagnoses of urolithiasis and stroke relied on administrative claims data recorded by physicians in the data set. To maximise case ascertainment, we adopted strict definitions of urolithiasis and stroke and required that diagnoses were made by specialists.
Second, the urolithiasis cohort had more comorbidities that are well known risk factors for stroke; however, the NHIRD does not provide data on the treatment status of these comorbidities. In addition, the mention of chronic infection due to urolithiasis and the record of blood pressure variability were not included in the NHIRD. Therefore, the severity and control conditions of the participants’ hypertension, diabetes mellitus, hyperlipidaemia and the status of chronic infection due to urolithiasis could not be determined. Third, individual patient information related to stroke – including family history, personal tobacco use habits and lifestyle factors – were not available in the NHIRD.

Finally, despite the temporal relationship between urolithiasis and stroke, the underlying causal mechanism was not definitively confirmed in this retrospective study. Urolithiasis shares the comorbidities and pathophysiology of stroke and may suggest the process of cerebral atherosclerosis. Determining whether urolithiasis predisposes a patient to subsequent stroke directly or whether other common factors, such as comorbidities, oxidative stress, inflammation and vascular theory of the formation of urolithiasis, contribute to urolithiasis earlier in life and develop into stroke later is difficult. Additional prospective studies are warranted to investigate the mechanisms and validate the effects of urolithiasis on the risk of stroke.

**Conclusion**

The present study detected an increased risk of both ischaemic and haemorrhagic stroke in patients with urolithiasis compared with those without, particularly in those older than 40 years. To decrease the health burden and risk of disability from further stroke, physicians should consider patients with urolithiasis as a high-risk group for stroke. Early lifestyle modifications and interventions for the control of comorbidities may be beneficial for the reduction of stroke risk in patients with urolithiasis.

**References**


Non-diabetic renal disease in patients with type 2 diabetes: a single centre study
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Key words
diabetic nephropathy, diabetic retinopathy, non-diabetic renal disease, renal biopsy, type 2 diabetes mellitus.

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Abstract
Background: Non-diabetic renal disease (NDRD) has been widely known in diabetic patients. The clinical differentiation between diabetic nephropathy (DN) and NDRD is still not so clear and effective.
Aim: To analyse the pathological characteristics and distribution of renal injury in selected type 2 diabetic patients. Comparison between DN and NDRD in clinical characteristics, to find important predictors for NDRD.
Methods: To conduct retrospective analysis of clinical, laboratory and pathohistological data of type 2 diabetic patients in whom renal biopsies were performed from March 2010 to September 2014 in Shandong Provincial Hospital affiliated to Shandong University (n = 88).
Results: According to the findings of renal biopsy, the incidences of DN, NDRD and DN complicated with NDRD were 20.46, 72.73 and 6.82% respectively. The most common NDRD found were: membranous nephropathy, followed by IgA nephropathy and focal segmental glomerulosclerosis. In multivariate logistic-analysis, fasting blood glucose (odds ratio (OR) 0.714; 95% confidence interval (CI) = 0.543–0.939; P = 0.016) and absence of diabetic retinopathy (OR 18.602; 95% CI = 2.176–159.018; P = 0.003) were independent predictors of NDRD.
Conclusions: This study confirmed a considerably high prevalence of NDRD in type 2 diabetic patients with renal injury. As some cases of NDRD are readily treatable or remittable, we should consider renal biopsy in selected diabetic patients with renal involvement, especially in those with effective blood glucose control and the absence of diabetic retinopathy.

Introduction
Type 2 diabetes mellitus with increasing incidence has become one of the most important health problems worldwide. Diabetic nephropathy (DN) is a very common complication of diabetes and has been the first cause of end-stage renal disease in developed countries, meanwhile the number is increasing year by year in China too. However, DN in diabetic patients is not the only form of the kidney injury. The other injury forms apart from the DN are collectively referred to as non-diabetic renal disease (NDRD). Different from DN, NDRD includes a variety of kidney damage forms. There are significant heterogeneity in clinical, pathological features and prognosis between DN and NDRD. Clinical and pathological diagnosis of these diseases has decisive influence on the selection of the treatment, and thus affects renal prognosis of patients eventually. However, the diagnosis method for this kind of patient is not uniform.

The diagnosis of DN is almost always based on clinical grounds and supported by persistent proteinuria, hypertension and a progressive decline in renal function, while renal biopsy is not always necessary. By contrast, patients with potential NDRD are frequently overlooked. Treatments for DN and NDRD are also quite different. It is generally believed that it is difficult to reverse DN, whereas some cases of NDRD are readily treatable, even remittable. As is generally known, renal biopsy is the most important way to identify DN or NDRD. Taking into account the large trauma caused by renal biopsy, we may usually undertake renal biopsy in patients with indications of NDRD. However, the role of renal biopsy in diabetic patients with signs and symptoms of kidney disease is still controversial. Therefore, related studies need to be carried out to find predictors for NDRD.

Funding: None.
Conflict of interest: None.
Methods

This retrospective study was conducted by reviewing the medical records of Type 2 diabetic patients who underwent percutaneous renal biopsy at Shandong provincial hospital affiliated to Shandong University (Jinan, China) between March 2010 and September 2014. All patients were diagnosed at the time of biopsy with type 2 diabetes as defined by the World Health Organization and the American Diabetes Association. Biopsy indications were uniform based on clinically strong suspicion of NDRD according to the following categories: sudden onset of heavy proteinuria, unexplained rapidly progressive renal failure, persistent glomerular haematuria and absence of diabetic retinopathy.

The following clinical data were collected for each patient: age, sex, duration of diabetes prior to biopsy, presence of hypertension, presence of diabetic retinopathy and presence of cardiac injury. Additional laboratory parameters, such as levels of serum creatinine, blood urea nitrogen, uric acid, cystatin C, serum albumin, serum cholesterol, triglyceride, fasting blood glucose, maximal 24-h proteinuria, presence of glomerular haematuria were also collected. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive medications. Diabetic retinopathy was diagnosed by direct ophthalmoscopy performed by an ophthalmologist. Cardiac injury was determined by a cardiologist according to the results of cardiac ultrasound. Hematuria was defined as >3 red blood cells per high power microscope field in a centrifuged urine sample. The collection of laboratory data of all the included patients is based on the materials at the second morning after hospitalisation.

The present study was approved by the ethics committee of Provincial Hospital Affiliated to Shandong University. Written consent was obtained from all patients before the renal biopsy performed. Light microscopy, immunofluorescence and electron microscopy were performed in all cases. All biopsy specimens were reviewed by two experienced and independent pathologists.

Pathological reports were reviewed and patients were classified into three groups: patients with isolated NDRD, patients with DN complicated with NDRD and patients with isolated DN. Furthermore, another classification group was created on the basis of having NDRD (i.e. NDRD vs non-NDRD patients).

Statistical analysis

Normally distributed data were expressed as mean ± SD, skewed data as median with interquartile range; categorical data were reported as frequency (%). The independent t-test or analysis of variance was used to compare normally distributed continuous variables. Between-group differences in data for skewed distributed variables were analysed using the Mann–Whitney U-test or Kruskal–Wallis test. The Chi-squared test was used to compare categorical variables. In order to determine independent predictors for DN and for NDRD, multiple logistic regression using forward stepwise method was performed, including the covariates with a P-value of <0.05 in univariate analysis. Receiver operating characteristic (ROC) curves were constructed for significant variables of NDRD. Area under curves (AUC) (the areas under the ROC curves) were calculated for determining sensitivity and specificity of predictors. A two-sided P-value of <0.05 was considered to indicate statistical significance. SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA) was used for all analysis.

Results

A total of 88 Chinese patients with type 2 diabetes was included in this study. Mean age at biopsy was 49.3 ± 11.9 years, 57 cases (65%) were male and median duration of diabetes was 36.8 ± 42.9 months (ranging from 2 to 168 months). The baseline clinical and laboratory data are summarised in Table 1.

According to the result of renal biopsy, 64 patients (72.73%) were diagnostic of NDRD, 18 patients (20.45%) revealed isolated DN and 6 patients (6.81%) showed DN complicated with NDRD. The most common NDRD was membranous nephropathy in 36 patients (51.4%), followed by IgA nephropathy (14.3%) and focal segmental glomerulosclerosis (FSGS) (10.0%) as shown in Table 2.

In univariate analysis, significant differences were confirmed in classification groups (DN vs mixed lesions vs NDRD, Table 1) regarding age (P = 0.015), diabetes duration (P < 0.000), cystatin C (P = 0.001), serum creatinine (P = 0.014), blood urea nitrogen (P = 0.007), fasting blood glucose (P < 0.000), presence of hypertension (P = 0.027) and presence of diabetic retinopathy (P < 0.000). Comparison between NDRD with non-NDRD revealed that NDRD-patients had lower fasting blood glucose (P < 0.000), less presence of diabetic retinopathy (P < 0.000) and less presence of hypertension (P = 0.008) (Table 3).

Multivariate logistic regression analysis of the variables found statistically significant in univariate analysis above was used to determine risk factors closely related to NDRD. Table 4 shows the result. Significant risk factors for NDRD were fasting blood glucose (odds ratio (OR) 0.714; 95% confidence interval (CI) = 0.543–0.939; P = 0.016) and the absence of diabetic retinopathy.
Table 1 Clinical and biochemical characteristics of the study patients in total and in classification groups (isolated DN vs mixed lesions vs isolated NDRD)

<table>
<thead>
<tr>
<th></th>
<th>ALL (n = 88)</th>
<th>DN (n = 18)</th>
<th>MIX (n = 6)</th>
<th>NDRD (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.3 ± 11.9</td>
<td>47.4 ± 12.0</td>
<td>62.7 ± 8.6</td>
<td>48.5 ± 11.6</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>57 (65%)</td>
<td>12 (66.7%)</td>
<td>3 (50%)</td>
<td>42 (58.3%)</td>
</tr>
<tr>
<td>Diabetes duration (months)</td>
<td>36.8 ± 42.9</td>
<td>52.8 ± 50.4</td>
<td>114 ± 55.2</td>
<td>25.2 ± 28.8</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>8.97 ± 2.26</td>
<td>10.85 ± 2.43</td>
<td>9.98 ± 2.28</td>
<td>8.34 ± 1.88</td>
</tr>
<tr>
<td>24-h proteinuria (g)</td>
<td>4.39 ± 2.74</td>
<td>4.35 ± 3.21</td>
<td>6.07 ± 2.02</td>
<td>4.25 ± 2.64</td>
</tr>
<tr>
<td>Serum albumins (g/L)</td>
<td>30.8 ± 6.2</td>
<td>29.1 ± 6.8</td>
<td>21.1 ± 8.1</td>
<td>28.5 ± 9.1</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/L)</td>
<td>8.11 ± 3.50</td>
<td>6.64 ± 1.73</td>
<td>12.37 ± 6.17</td>
<td>8.12 ± 3.28</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>3.02 ± 2.82</td>
<td>2.19 ± 0.80</td>
<td>3.49 ± 1.47</td>
<td>3.20 ± 3.23</td>
</tr>
<tr>
<td>BUN (mmol/L)*</td>
<td>7.37 ± 4.16</td>
<td>9.69 ± 5.79</td>
<td>9.08 ± 2.82</td>
<td>6.56 ± 3.43</td>
</tr>
<tr>
<td>Scr (μmol/L)</td>
<td>92.4 ± 61.3</td>
<td>112.9 ± 58.1</td>
<td>109.8 ± 42.7</td>
<td>80.3 ± 26.7</td>
</tr>
<tr>
<td>Uric acid (μmol/L)</td>
<td>380.4 ± 108.9</td>
<td>372.6 ± 140.3</td>
<td>356.3 ± 115.2</td>
<td>384.9 ± 99.6</td>
</tr>
<tr>
<td>Cystatin C (mg/L)*</td>
<td>1.35 ± 0.66</td>
<td>1.78 ± 1.14</td>
<td>1.73 ± 0.13</td>
<td>1.19 ± 0.39</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>44 (50.0%)</td>
<td>14 (77.8%)</td>
<td>2 (33.3%)</td>
<td>28 (43.8%)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>38 (43.2%)</td>
<td>8 (44.4%)</td>
<td>2 (33.3%)</td>
<td>28 (43.8%)</td>
</tr>
<tr>
<td>Diabetic retinopathy*</td>
<td>20 (22.7%)</td>
<td>12 (66.7%)</td>
<td>5 (83.3%)</td>
<td>3 (4.7%)</td>
</tr>
<tr>
<td>Cardiac injury</td>
<td>3 (3.4%)</td>
<td>2 (11.1%)</td>
<td>1 (16.7%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*P < 0.05 (ANOVA/Kruskal-Wallis test)² test/Fisher’s test). ANOVA, analysis of variance; BUN, blood urea nitrogen; DN, diabetic nephropathy; FBG, fasting blood glucose; MIX, NDRD superimposed on DN; NDRD, non-diabetic renal disease; Scr, serum creatinine.

(OR 18.602, 95% CI = 2.176–159.018; P = 0.003). ROC analysis was used to evaluate sensitivity and specificity of those risk factors closely related to NDRD, and results are summarised in Table 5. For NDRD, fasting blood glucose of <9.88 mmol/L (cut-off value (0.778, 0.186)) showed highest AUC. The AUC curves of the predictors for NDRD are shown in Figure 1.

Discussion

Currently, the occurrence of NDRD in diabetic patients is well recognised. In the present study, the prevalence of NDRD in diabetic patients was 73.73%. Previous studies demonstrated that the prevalence varies between 8 and 93.5%.4,3,6–21 Our finding was similar to the result of Kharrat et al. (69.5%).17 The differences in the incidence of NDRD may be caused by the differences in patients selected (geographical and ethnic differences) and biopsy selection criteria. Our indications for renal biopsy are consistent with the common indications in reported studies, including rapidly progressive renal failure,9,10,12–14,18 proteinuria,4,8,12–17,18 glomerular haematuria9–13,17–19 and absence of diabetic retinopathy.4,5,9,14–16,19

The renal disease spectra of NDRD are not the same, glomerulonephritis are reported as the most common NDRD in the majority of other studies,5,10–16 which is in agreement with our findings. On the other hand, some studies reported the most common NDRD was interstitial nephritis,17,18 In our study, membranous nephropathy was found to be the most common glomerulonephritis (51.4%), followed by IgA nephropathy and FSGS. Other pathological types like minimal change disease, hypertensive nephrosclerosis were also found in our study. The pathological characteristics of NDRD were summarised by Kumar et al.22 according to previous studies. The most common NDRD in the United States, Korea and Iraq were FSGS, IgA nephropathy and membranous proliferative glomerulonephritis, respectively, while acute interstitial nephritis and post infection

Table 2 Pathological findings in non-diabetic renal disease

<table>
<thead>
<tr>
<th>Type of NDRD</th>
<th>All (n = 70)</th>
<th>MIX (n = 6)</th>
<th>NDRD (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranous nephropathy</td>
<td>36 (51.4%)</td>
<td>4 (66.7%)</td>
<td>32 (50%)</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>10 (14.3%)</td>
<td>2 (33.3%)</td>
<td>8 (12.5%)</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>7 (10.0%)</td>
<td>0</td>
<td>7 (10.9%)</td>
</tr>
<tr>
<td>Mesangial proliferative glomerulonephritis</td>
<td>6 (8.6%)</td>
<td>0</td>
<td>6 (9.4%)</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>6 (8.6%)</td>
<td>0</td>
<td>6 (9.4%)</td>
</tr>
<tr>
<td>Hepatitis B virus associated glomerulonephritis</td>
<td>2 (2.9%)</td>
<td>0</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Hypertensive nephrosclerosis</td>
<td>2 (2.9%)</td>
<td>0</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>1 (1.4%)</td>
<td>0</td>
<td>1 (1.6%)</td>
</tr>
</tbody>
</table>

MIX, NDRD superimposed on DN; NDRD, non-diabetic renal disease.
For NDRD, the prediction of diabetic retinopathy and absence of hypertension were found to be significant risk factors for NDRD in univariate analysis (NDRD vs non-NDRD). In multivariate analysis, only the fasting blood glucose of <9.88 mmol/L and the absence of diabetic retinopathy were considered to be significant independent predictors for NDRD.

In most previous studies, absence of diabetic retinopathy was found to be a significant predictor for NDRD in univariate or multivariate analysis.10-12,16,18,20 This finding therefore confirms the accepted view that absence of diabetic retinopathy indicates the possibility of NDRD, thus warranting a renal biopsy. In this study, sensitivity (88.57%) of the absence of diabetic retinopathy in prediction of NDRD was higher than the results of Mou et al.11 and Wong et al.20 However, the specificity (66.67%) in this study was lower compared with other two studies.

Fasting blood glucose of <9.88 mmol/L was another significant predictor for NDRD in this study, its sensitivity and specificity were found to be 81.43 and 77.78% respectively. This predictor has not been reported in published studies. Despite that the fasting blood glucose was collected uniformly at the second morning after hospitalisation, blood glucose is affected by some inevitable factors. Due to the limitation of this study, we could consider fasting blood glucose as an important reference rather than a decisive predictor. On the other hand, lower serum HbA1c levels12 and independence of insulin therapy20,21 were found to be significant predictors of NDRD in recent studies. Consequently, comprehensive analysis of blood glucose control (lower fasting blood glucose and serum HbA1c levels, reasonable insulin therapy) should raise the possibility of NDRD.

In this study, there were no other clinical or laboratory variables found statistically significant or predictive for NDRD in multivariate analysis. Nevertheless, absence of hypertension that has statistical significance in univariate

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**Table 3** Clinical and biochemical characteristics of the study patients in the classification group (NDRD vs non-NDRD)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>NDRD (n = 70)</th>
<th>non-NDRD (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.7 ± 12.0</td>
<td>47.4 ± 12.0</td>
<td>0.485</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>45 (64.3%)</td>
<td>12 (66.7%)</td>
<td>0.850</td>
</tr>
<tr>
<td>Diabetes duration (months)</td>
<td>32.8 ± 40.32</td>
<td>52.8 ± 50.4</td>
<td>0.076</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>8.48 ± 1.96</td>
<td>10.85 ± 2.43</td>
<td>0.000</td>
</tr>
<tr>
<td>24-h proteinuria (g)</td>
<td>4.41 ± 2.63</td>
<td>4.35 ± 3.21</td>
<td>0.937</td>
</tr>
<tr>
<td>Serum albumins (g/L)</td>
<td>27.8 ± 9.2</td>
<td>29.1 ± 6.8</td>
<td>0.602</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/L)</td>
<td>8.49 ± 3.74</td>
<td>6.64 ± 1.73</td>
<td>0.072</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>3.22 ± 3.11</td>
<td>2.19 ± 0.80</td>
<td>0.168</td>
</tr>
<tr>
<td>BUN (mmol/L)</td>
<td>6.78 ± 3.45</td>
<td>9.69 ± 5.79</td>
<td>0.087</td>
</tr>
<tr>
<td>Scr (μmol/L)</td>
<td>82.8 ± 29.2</td>
<td>112.9 ± 58.1</td>
<td>0.073</td>
</tr>
<tr>
<td>Uric acid (μmol/L)</td>
<td>382.4 ± 100.4</td>
<td>372.6 ± 140.3</td>
<td>0.734</td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>1.24 ± 0.41</td>
<td>1.78 ± 1.14</td>
<td>0.059</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>30 (42.9%)</td>
<td>14 (77.8%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hematuria</td>
<td>30 (42.9%)</td>
<td>8 (44.4%)</td>
<td>0.218</td>
</tr>
<tr>
<td>Diabetic retinopathy*</td>
<td>8 (11.4%)</td>
<td>12 (66.7%)</td>
<td>0.072</td>
</tr>
<tr>
<td>Cardiac injury</td>
<td>1 (1.4%)</td>
<td>2 (11.1%)</td>
<td>0.105</td>
</tr>
</tbody>
</table>

*P < 0.05 (ANOVA/Mann–Whitney test)*2 test/Fisher’s test. ANOVA, analysis of variance; BUN, blood urea nitrogen; FBG, fasting blood glucose; NDRD, non-diabetic renal disease; Scr, serum creatinine.

---

**Table 4** Multivariate logistic regression analysis of diabetic kidney disease and of non-diabetic renal disease

<table>
<thead>
<tr>
<th>Indicator</th>
<th>β-Estimate</th>
<th>Standard error</th>
<th>Wald (χ²)</th>
<th>P-value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>For NDRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>−0.337</td>
<td>0.142</td>
<td>5.827</td>
<td>0.016</td>
<td>0.714</td>
<td>0.543–0.939</td>
</tr>
<tr>
<td>Diabetic retinopathy (no vs yes)</td>
<td>2.923</td>
<td>1.095</td>
<td>7.130</td>
<td>0.008</td>
<td>18.602</td>
<td>2.176–159.018</td>
</tr>
</tbody>
</table>

CI, confidence interval; FBG, fasting blood glucose; OR, odds ratio.

---

**Table 5** Sensitivity, specificity, positive and negative predictive values of significant variables in the prediction of diabetic kidney disease and of non-diabetic renal disease

<table>
<thead>
<tr>
<th>Prediction</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>For NDRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBG (&lt;9.88 mmol/L)</td>
<td>0.798</td>
<td>81.43</td>
<td>77.78</td>
<td>93.44</td>
<td>51.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetic retinopathy (no)</td>
<td>0.776</td>
<td>88.57</td>
<td>66.67</td>
<td>91.18</td>
<td>60.00</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AUC, area under curve; FBG, fasting blood glucose; NPV, negative predictive value; PPV, positive predictive value.
analysis was found as a significant predictor of NDRD in the study by Zhou et al.\textsuperscript{12} In addition, haematuria,\textsuperscript{4,12,16,17} serum creatinine or estimated glomerular filtration rate (eGFR),\textsuperscript{4,11,12,14,16} proteinuria\textsuperscript{4} were all found as significant factors for the identification of NDRD in published studies respectively.

Identifying and monitoring DN relies upon assessments of kidney function, usually with an eGFR <60 mL/min/1.73 m\(^2\), and kidney damage, usually by estimation of albuminuria >30 mg/g creatinine.\textsuperscript{24} Several post studies revealed that long duration of diabetes, the presence of diabetic retinopathy and poor glycaemic control may correlate with DN.\textsuperscript{5,10,12,24–26} Combination with the results of this study, diabetic retinopathy and glycaemic control are significant predictors for the identification of NDRD and DN.

There were some limitations of this study, such as retrospective design, relative small sample size and biases in selecting patients, which might cause ascertainment error, recall or lead-time biases. Data on some clinical variables (HbA1c levels, BMI, etc.) and characteristics were not available for some patients and thus could not be included in our analysis. The exact duration of type 2 diabetes could not be established in each case due to incomplete health examination procedures in some areas. As only type 2 diabetic adults with suspicion of NDRD were enrolled, bias in selecting patients is another important limitation in our study. As shown, there was high heterogeneity with respect to the criteria used for undertaking renal biopsy, so it is important to identify clinical predictors of NDRD. Recognised indications of NDRD were chosen as the criteria of renal biopsy. However, these limitations might still hamper the possibility of drawing definitive conclusions to the entire diabetic population.

**Conclusion**

There is a high incidence of NDRD in type 2 diabetic patients with renal injury who will benefit from an early diagnosis followed by an appropriate disease specific therapy. Renal biopsy is necessary for suspected NDRD patients with the indications, including rapidly progressive renal failure, proteinuria and effective blood glucose control, particularly the absence of diabetic retinopathy. By this strategy, we could improve their kidney survival and potentially reduce the burden of chronic kidney disease in this population.\textsuperscript{15}

**References**


BRIEF COMMUNICATIONS

Impact of limited English proficiency on presentation and outcomes of patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction

Sinjini Biswas,1,2,3 Michael Seman,1 Nicholas Cox,1,4 Christopher Neil,1 Angela Brennan,2 Diem Dinh,2 Antony Walton,1,3 William Chan,1,3 Jeffrey Lefkovits,2,5 Christopher Reid2,6 and Dion Stub1,2,3,7

1Department of Cardiology, Western Health, 2Department of Epidemiology and Preventive Medicine, Monash University, 3Department of Cardiovascular Medicine, The Alfred Hospital, 4Department of Medicine – Western Health, The University of Melbourne, 5Department of Cardiology, Royal Melbourne Hospital, and 7Cardiac Arrest Research Group, Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, and 6NHMRC Centre of Research Excellence in Cardiovascular Outcomes Improvement, Curtin University, Perth, Western Australia, Australia

Key words
acute myocardial infarction, English proficiency, percutaneous coronary intervention.

Abstract
Doctor–patient language discordance has been shown to lead to worse clinical outcomes. In this study of patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction at an Australian health service, we demonstrated that limited English proficiency (LEP) is an independent predictor of prolonged symptom-to-door time, but does not lead to worse 30-day mortality compared with English-proficient patients. More effort needs to be placed in providing public health education in varied languages to encourage early presentation to hospital for patients with LEP.

Increasing global migration leading to cultural and linguistic diversity in society has presented challenges in healthcare delivery, as a growing problem of language discordance between healthcare providers and patients arises. In Australia, recent census data have shown that over one-quarter of Australia’s population was born overseas and nearly one-fifth of the population speak a language other than English at home.1 Language barriers can compromise patient–provider communication and negatively affect the ability to deliver safe and effective healthcare.2,3 Previous studies have shown that in predominantly English-speaking countries, limited English proficiency (LEP) is associated with prolonged hospital length of stay, higher readmission rates and poorer self-reported health status.4–8 Within cardiology practice, patients with LEP have been shown to have lower rates of cardiac catheterisation and percutaneous coronary intervention (PCI) following presentation with an acute coronary syndrome (ACS).9 However, the impact of LEP ondelays to cardiac catheterisation and outcomes in patients with ST-elevation myocardial infarction (STEMI) treated with PCI has not been specifically investigated. In this study, we aimed to examine whether among patients with STEMI undergoing primary PCI, LEP was associated with longer delays to reperfusion and worse clinical outcomes.

This study was performed at a multi-centre tertiary health service in Melbourne, Australia. The health service treats one of the most culturally diverse communities in the state of Victoria, with 38% of the population speaking a language other than English at home.1 Routinely collected data on all patients undergoing PCI includes baseline demographics, procedural information, in-hospital complications and 30-day follow-up events as part of the Victorian Cardiac Outcomes Registry (VCOR) – a multi-centre state-wide PCI registry, including all public and private hospitals in Victoria, Australia which has been described previously.10,11 All patients are provided with

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Conflict of interest: None.
information on the VCOR data collection process and there is an opt-out consent process, with no patients at this health service having declined involvement to date. In this study, all STEMI patients undergoing primary PCI at this health service between 15 July 2013 and 31 December 2016 were included and data collected as part of VCOR were analysed. Patients who had PCI post-thrombolysis or had an in-hospital STEMI were excluded.

In this study, the health service’s patient administration system database was used to identify the patient’s primary spoken language and country of birth. These data are documented at the time of hospital admission by a clerk and checked at each subsequent hospital attendance. Patients who identified a language other than English as their primary spoken language were defined as having LEP. All patients who identified English as their primary spoken language were defined as English proficient (EP).

Data for continuous variables were expressed as means and standard deviations whilst categorical variables were expressed as numbers of people and percentages. Categorical variables were compared using the Chi-squared test or the Fisher exact test. Continuous variables were compared using the t-test or Mann Whitney U-test. Logistic multi-variable regression analysis was used to identify independent predictors of prolonged symptom-to-door time using variables with a P-value of less than 0.1 on univariate analysis. A two-sided P-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM spss statistics software version 24 (IBM, Armonk, NY, USA).

The study was reviewed and granted ethical approval by the ethics committee at Western Health.

During the study period, 650 patients underwent primary PCI for STEMI and were included in this study. Of this, 98 patients (15.1%) were classified as LEP based on their self-reported primary spoken language. Among the LEP patients, the most commonly spoken languages were Vietnamese (23.4%, n = 23) and Greek (8.2%, n = 8). Of the EP patients, 195 (35.3%) were born outside of Australia, New Zealand, the United Kingdom or North America.

The LEP group was slightly older (mean age 65.6 years vs 58.8 years, P < 0.01) with a greater proportion of females (31.6% vs 19.2%, P < 0.01). There were no other significant differences in baseline demographics and comorbidities, including in the history of previous PCI or coronary artery bypass graft surgery (Table 1). Presentation with out-of-hospital cardiac arrest or cardiogenic shock was similar in the two groups. Pre-hospital notification by paramedics was also similar. There were no significant procedural differences in terms of PCI success, use of drug-eluting stents or lesion complexity between the groups.

Door-to-balloon times were similar in both the LEP and EP groups (71 min (interquartile (IQR) 48–112) vs

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of baseline and procedural characteristics and outcomes in English proficient and limited English-proficient patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>English proficient (EP)</td>
</tr>
<tr>
<td>Number</td>
<td>552</td>
</tr>
<tr>
<td>Mean age ± SD (years)</td>
<td>58.8 ± 12.7</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>446 (80.8)</td>
</tr>
<tr>
<td>Mean body mass index (kg/m²)</td>
<td>28.8 ± 5.8</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>94 (17.0)</td>
</tr>
<tr>
<td>Stage 4–5 chronic kidney disease (estimated glomerular filtration rate &lt; 30 mL/min/1.73 m²), n (%)</td>
<td>12 (2.2)</td>
</tr>
<tr>
<td>Previous percutaneous coronary intervention, n (%)</td>
<td>63 (11.4)</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft surgery, n (%)</td>
<td>9 (1.6)</td>
</tr>
<tr>
<td>Out-of-hospital cardiac arrest, n (%)</td>
<td>35 (6.3)</td>
</tr>
<tr>
<td>Cardiogenic shock on presentation, n (%)</td>
<td>59 (10.7)</td>
</tr>
<tr>
<td>Pre-hospital notification, n (%)</td>
<td>293 (53.1)</td>
</tr>
<tr>
<td>Radial access, n (%)</td>
<td>271 (49.1)</td>
</tr>
<tr>
<td>AHA/ACC type B2/C lesion, n (%)</td>
<td>303 (54.9)</td>
</tr>
<tr>
<td>Drug-eluting stent used, n (%)</td>
<td>359 (65.0)</td>
</tr>
<tr>
<td>Successful percutaneous coronary intervention, n (%)</td>
<td>527 (95.5)</td>
</tr>
<tr>
<td>Length of stay in days, median (IQR)</td>
<td>3 (3–3)</td>
</tr>
<tr>
<td>In-hospital mortality, n (%)</td>
<td>29 (5.3)</td>
</tr>
<tr>
<td>In-hospital major adverse cardiac events, n (%)</td>
<td>32 (5.8)</td>
</tr>
<tr>
<td>In-hospital bleeding (BARC type 2 or more), n (%)</td>
<td>16 (2.9)</td>
</tr>
<tr>
<td>30-Day mortality, n (%)</td>
<td>37 (7.8)</td>
</tr>
<tr>
<td>30-Day unplanned readmissions, n (%)</td>
<td>46 (9.7)</td>
</tr>
</tbody>
</table>

ACC, American College of Cardiology; AHA, American Heart Association.
68 min (IQR 44–103), \( P = 0.21 \). Total ischaemic time defined as time from symptom onset to first balloon inflation in a coronary artery was significantly longer in the LEP group (281 min (IQR 160–720) vs 203 min (IQR 150–350), \( P < 0.01 \)), driven by longer symptom-to-door times (193 min (IQR 94–502) vs 120 min (IQR 85–226), \( P < 0.01 \)) (Fig. 1). Median symptom-to-door time (STDT) for the entire cohort was 124 min. Patients with a STDT greater than 124 min were considered to have a prolonged STDT. On multiple logistic regression analysis, LEP was an independent risk factor for prolonged STDT (odds ratio (OR) 1.63, 95% confidence interval (CI) 1.05–2.54; \( P = 0.03 \)) whilst a history of PCI or coronary artery bypass graft surgery (OR 0.50, 95% CI 0.30–0.83; \( P < 0.01 \)) and pre-hospital notification (OR 0.64, 95% CI 0.47–0.87; \( P < 0.01 \)) were found to be independent protective factors for prolonged STDT.

The median length of hospital stay was equal between the two groups at 3 days (\( P = 0.70 \)). There was no difference in in-hospital mortality and major adverse cardiac events (MACE) between the two groups (7.1% vs 5.3%, \( P = 0.45 \) and 7.1% vs 5.8%, \( P = 0.61 \) respectively). A total of 85.5% in the EP group and 89.8% in the LEP group had 30-day follow up completed (\( P = 0.26 \)). There was no significant difference in 30-day mortality (\( P = 0.69 \)) or unplanned readmissions (\( P = 0.85 \)) between the two groups.

**Discussion**

In our study, we found a marked difference in symptom-to-door time between LEP and EP patients, with median symptom-to-door time being 73 min longer in LEP patients. LEP was also found to be an independent predictor of prolonged symptom-to-door time. However, once patients entered the hospital system, there were no apparent differences in treatment times or outcomes. In-hospital and 30-day mortality were both slightly higher in the LEP group, but these differences were not statistically significant, possibly due to a small sample size.

Recent focus in STEMI care has been on reducing delays to reperfusion by both encouraging patients to present early and improving systems of care of STEMI management. In Australia, the National Heart Foundation health promotion organisation has for many years run a media campaign to educate the public on potential symptoms of an acute myocardial infarction (AMI). Yet the significantly longer symptom-to-door time in LEP patients however suggests that knowledge on AMI symptoms may be deficient in the LEP population. This has also been demonstrated in the United States where knowledge on stroke and AMI symptoms was found to be lower in Spanish-speaking Hispanics compared with all other English-speaking racial groups. Other American studies have also found longer delays to treatment for AMI for Hispanics than for non-Hispanic Caucasian
Americans. Potential barriers to seeking early treatment for LEP patients in our study may have been a reluctance to call for urgent ambulance services for cultural reasons, language barriers as well as concerns about cost. Strategies to improve knowledge in communities with a high proportion of LEP with targeted education are needed.

In this study the delays to presentation did not translate to an increased length of stay in LEP patients. Data from the CONCORDANCE registry comparing LEP and EP patients with ACS showed longer length of stay, as well as higher in-hospital and 6-month mortality in the LEP group. Similarly an older Australian study comparing outcomes by English-speaking background also found a longer average length of stay in the non-English-speaking group; however, this study divided patients according to country of birth rather than language preference, which may have affected the results. However, a large American study of MI patients by Grubbs et al. showed that length of stay and in-hospital mortality were not higher in LEP patients when adjusted for receipt of cardiac catheterisation or surgery. STEMI care is much more streamlined than care of non-ST elevation ACS and our study only included those undergoing PCI which may explain the similarity between our results and those of Grubbs et al. Streamlining of STEMI management with PCI and the use of clinical pathways with a checklist approach, such as those used across our health network, is likely to be an important contributor in ensuring that equal care is provided to all patients regardless of English-speaking capacity. Implementing similar care pathways in other areas of cardiology and healthcare in general may help to ensure LEP patients are not disadvantaged in their care.

There are several limitations to our study. There is no standardised tool to assess English proficiency status in the published literature and previous studies have used varying mechanisms to assess this ranging from using the language spoken in the patients’ country of birth only, to using patients’ self-reported language preference at different times in the hospital admission. We performed our analysis based on patients’ self-identification of their primary spoken language, which does not take into account their fluency, particularly in the EP group, which may affect patient care and understanding. In addition, similar to other studies, patients in our study were dichotomised into LEP and EP groups, whilst in reality English proficiency is much more of a continuum. As the registry did not collect data on ambulance utilisation, we were unable to compare this between the groups. The sample size in this study was also small and not adequately powered for assessing differences in mortality and MACE. As a result, we could not adequately adjust for baseline differences, including unmeasured variables, such as socio-economic status and educational level, which may have confounded the impact of English proficiency. The results therefore should be validated in a larger cohort in the future.

In conclusion, LEP was associated with significantly longer symptom-to-door time, but similar door-to-balloon times, in-hospital and 30-day mortality, compared with English-proficient patients in our study of STEMI patients undergoing primary PCI. Whilst it is reassuring that STEMI systems of care are robust such that LEP patients are not disadvantaged within the health system, these results highlight the need for better education about cardiovascular emergencies targeted to non-English-speaking communities.

References


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Clinical features and outcome of patients with cutaneous melioidosis during a nosocomial outbreak in a temperate region of Australia

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Key words

cutaneous melioidosis, Burkholderia pseudomallei, nosocomial outbreak, meropenem infusions

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Melioidosis is caused by the Gram-negative bacillus *Burkholderia pseudomallei*, an environmental organism endemic to northern Australia and southeast Asia between the latitudes of 20°N and 20°S. Outside of these areas, melioidosis is thought to occur rarely.1 In Australia, the endemic boundaries of melioidosis are less clear, but in addition to reports of isolated animal and human cases related to the traffic of livestock from the northern Australia,2 there is evidence of local acquisition of melioidosis in subtropical and desert areas south of 20°S, especially following heavy rain events.3,4 Transmission of *B. pseudomallei* usually occurs following contact with soil or water containing the bacterium during occupational or recreational activities. The clinical manifestations of melioidosis range from asymptomatic seroconversion, cutaneous infection, pneumonia,
multiple abscesses, severe septicemia and death. Severe cases often have underlying co-morbidities, such as diabetes, hazardous alcohol use and chronic renal disease.

Melioidosis is a notifiable disease in Western Australia (WA). Between January 2012 and November 2013, six cases of melioidosis were notified from Mandurah (latitude 32.5°S), a regional city with a population of 72 000 people situated 72 km south of the state capital, Perth. All were cutaneous infections affecting the limbs following the application of dressings to superficial injuries or chronic wounds that originated in the community. The laboratory aspects of the epidemiological investigation have been previously reported. Here, we present the clinical features, therapy and outcome for patients in this nosocomial outbreak of melioidosis from a non-endemic area.

The six cases were initially linked by their close geographical proximity to one another and similarities in clinical presentation. Data collected included clinical features, recent trauma or surgery, management of injury/wound prior to melioidosis diagnosis, previous travel or residence in tropical northern Australia, travel abroad, exposure to water and soil or potting mix during recreational or occupational activities, treatment and outcome following antibiotic therapy.

*B. pseudomallei* isolates were identified following culture from clinical specimens using the VITEK 2 system (bioMerieux, Marcy-l’Etoile, France). Species confirmation was obtained with Matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry and a panel of real-time polymerase chain reaction (PCR) assays. Multi-locus sequence typing (MLST) was performed using methods detailed elsewhere.

Case 1 occurred in January 2012, whilst Cases 2–6 were identified during the latter part of 2013. The only consistent epidemiological clue was that all cases had visited the same primary care practice prior to, or during the time of their illness.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Co-morbidities</th>
<th>Travel to endemic region</th>
<th>Mechanism of injury</th>
<th>Date of injury</th>
<th>Date of first dressing</th>
<th>Date of diagnosis</th>
<th>Outcome, side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85/F</td>
<td>T2DM renal impairment</td>
<td>Nil</td>
<td>Chronic venous ulceration</td>
<td>From 2005</td>
<td>20 January 2011</td>
<td>Successful</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50/M</td>
<td>Hypertension</td>
<td>Northern QLD (9 years ago)</td>
<td>SCC removal</td>
<td>26 August 2013</td>
<td>26 September 2013</td>
<td>Successful, headache with meropenem</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>80/F</td>
<td>T2DM</td>
<td>NT (34 years ago)</td>
<td>Pre-tibial skin tear</td>
<td>31 October 2013</td>
<td>31 October 2013</td>
<td>Successful</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>86/F</td>
<td>Nil</td>
<td>NT and Northern WA (21 years ago)</td>
<td>Pre-tibial skin tear</td>
<td>20 November 2013</td>
<td>29 November 2013</td>
<td>Successful</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>61/F</td>
<td>Nil</td>
<td>Nil</td>
<td>Forearm graze</td>
<td>2 September 2013</td>
<td>5 December 2013</td>
<td>Successful, intolerance to TMP/SMX</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>93/F</td>
<td>Nil</td>
<td>Nil</td>
<td>Pre-tibial skin tear</td>
<td>16 October 2013</td>
<td>13 December 2013</td>
<td>Successful</td>
<td></td>
</tr>
</tbody>
</table>

T2DM, type 2 diabetes mellitus; TMP/SMX, trimethoprim-sulfamethoxazole; WA, Western Australia.
driving to a refuse centre, or during recreational wood chopping in bushland around Mandurah. He was systemically well.

He received 2 weeks of intravenous meropenem (3 g/day; given through continuous infusion (CI)). Due to headache, malaise, and nausea that were subsequently attributed to meropenem, he underwent computerised tomography of his head to exclude intracerebral abscess. He then received trimethoprim/sulfamethoxazole to complete 3 months treatment with complete resolution of the infection.

Apart from Case 1, where the initial cutaneous lesion was a chronic left leg venous ulcer, the remaining cases occurred in women who sustained minor limb injuries. Cases 3, 4 and 6 sustained pre-tibial lacerations following trauma involving car doors or tow bars. Case 5 sustained a minor injury to her arm in a garden shed. None of the injuries was associated with significant soil contamination or water exposure (Fig. 1).

Like Case 2, they presented with delayed wound healing, increasing pain, erythema, and wound discharge and had dressings applied at their primary care practice. Wound swab samples grew *B. pseudomallei*, and isolates were sent to the reference lab for confirmation and MLST.

Clinical examination, chest radiography and routine blood tests, including full blood count and C-reactive protein, were performed and did not reveal evidence of disseminated infection or sepsis in any of the patients. All received 14 days of intravenous meropenem given by CI, followed by 10–12 weeks of oral antibiotics. Trimethoprim/sulfamethoxazole was prescribed for all initially. In one, this was changed to oral doxycycline due to gastrointestinal intolerance. All patients had complete resolution of infection with localised scarring and no further complications.

Once the primary care practice was identified as a possible source of infection, environmental sampling in and around the practice generated 62 samples, comprising surface swabs, wound dressing materials, fluids, ointments, creams, garden soil and building site soil. Only one grew *B. pseudomallei* (1.89 × 10³ CFU/mL); a previously opened 1000 mL bottle of saline irrigation fluid which had been in use from September 2013, but supplied to the practice in March 2013, well before Case 1. Unopened bottles from the same supplier batch were negative for *B. pseudomallei*. *Pseudomonas aeruginosa* was also present in the *B. pseudomallei*-contaminated irrigation fluid bottle.

**Discussion**

This nosocomial outbreak of melioidosis from a non-endemic area is the first such case series reported. Evidence linking the cutaneous melioidosis cases to a nosocomial source was established with a simple epidemiological investigation. MLST confirmed that the
six cases and the isolate from the contaminated saline shared a common sequence profile – ST1112.6

However, despite epidemiological and molecular similarities between Case 1 in 2012 and Cases 2–6 in late 2013, the source of B. pseudomallei remains unknown, and an epidemiological connection between Case 1 and the latter cases has yet to be established. Case 1 received wound care at the same health centre, prior to the arrival of the contaminated saline that was manufactured in March 2013.

Potential explanations for this temporal gap include the possibility that an unknown patient with chronic melioidosis has allowed multiple introductions of B. pseudomallei into medical products or a common external environmental reservoir. Manufacturing contamination prior to opening the saline bottle was unlikely because B. pseudomallei was not isolated from other opened and unopened bottles of the same batch of irrigation fluids. Furthermore, as the MLST isolate was most similar to isolates found in tropical Australia, rather than isolates found elsewhere in the world, this provides additional evidence against contamination during the manufacturing process of irrigation fluids imported from outside Australia. Similarly without the presence of any positive environmental sample, an explanation for how or why this infective agent has got into a bottle of wound irrigation fluid or even how it reached the temperate southwest of Australia remains elusive.

Nosocomial melioidosis is uncommon, but has occurred in both human and veterinary practice. Reports of urinary catheter associated infection7 and cutaneous disease in humans,10 and feline melioidosis, have occurred in melioidoid endemic settings as a consequence of exposure to soil near a health centre or directly from contaminated medical fluids. Though not a healthcare related exposure, the survival of B. pseudomallei in detergent and subsequent transmission has been reported in two mechanics working in tropical northern Australia that developed cutaneous melioidosis simultaneously.11 Autochthonous cases from non-endemic areas have also been described. As we have done in the present case series, where there are cryptic cases, the geographical region of origin can be inferred from MLST typing of the organism, without an apparent environmental source.12

Nosocomial outbreaks of other environmental Gram-negative organisms where contamination of antiseptics and disinfectants are the major source have been described.13 Like other environmental Gram-negative organisms, B. pseudomallei will tolerate a wide range of nutrient-free aqueous environments. As well as being able to survive in some antiseptic and detergent solutions, this organism can tolerate acid and hypertonic saline solutions, and refrigeration. The organism has been cultured from sterile distilled water stored for more than 16 years.14

As shown in the present case series, irrigation fluids manufactured for single use only were not disposed of immediately, thereby creating the environment for B. pseudomallei to survive and replicate. This situation may be more common in primary care where wound management is performed occasionally. The incidence of nosocomial infections associated with re-used irrigation fluids may therefore be higher than is appreciated, particularly if it involves common commensal bacteria. Here the outbreak was due to an unusual organism in a non-endemic area and its identification resulted in heightened awareness of the possibility of a point-source origin. With removal of the contaminated fluid and staff education, no further cases have been identified.

Cutaneous melioidosis has low mortality, but results in discomfort, inconvenience and costs to the health sector. All patients in the present study were successfully treated, but required a peripherally inserted central catheter and a prolonged course of IV meropenem through our ambulatory parenteral antibiotic programme. Whether there were specific bacterial virulence phenotypes or genetic polymorphisms15 to account for the absence of severe invasive disease remains the focus of further study of these isolates.

This cluster of six cutaneous melioidosis cases represents the largest nosocomial melioidosis outbreak to date, and highlights the potential for dissemination of B. pseudomallei and other Gram-negative bacteria in medical fluids widely used in routine healthcare procedures.

References
Diagnostic utility of an age-specific cut-off for d-dimer for pulmonary embolism assessment when used with various pulmonary embolism risk scores

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Key words
pulmonary embolism, risk scores, d-dimer, age.

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Pulmonary embolism (PE) is an important consideration in patients presenting to emergency department (ED) with dyspnoea with or without chest pain due to its significant morbidity and mortality. However, the non-specific and variable clinical presentation of PE creates diagnostic difficulty for clinicians, especially in older patients. Typical signs and symptoms such as dyspnoea and pleuritic chest pain are not as frequently reported in older populations, widening the spectrum of presentations for which PE must be considered. The recent recommended diagnostic workup of PE includes the sequential use of risk assessment and diagnostic tests. For patients with non-high clinical probability (as determined by a validated clinical risk score), a d-dimer assay can be used to rule out PE due to the high sensitivity of the test. However, d-dimer assays are not

Abstract
This retrospective cohort study compared the diagnostic utility (sensitivity, specificity and negative predictive value (NPV)) of the age-times-10 adjusted d-dimer cut-off used in combination with the original and simplified Well’s pulmonary embolism (PE) scores and the original and simplified revised Geneva scores to identify patients in whom PE is classified as unlikely according to each score. The PE risk scores performed similarly with high sensitivity (97.6, 97.1, 96.9 and 97.1% respectively) and NPV (99.3, 99.3, 99.2 and 99.2% respectively). Each missed only one PE. The age-times-10 age-adjusted d-dimer assay cut-off performed similarly with each of the clinical risk scores tested with high sensitivity and NPV.
highly specific for PE and may be elevated for several other reasons, including malignancy, trauma, inflammation or pregnancy. The standard d-dimer cut-off, < 500 μg/L, is able to exclude PE in about 30% of patients without the need for further imaging. Patients with a d-dimer score ≥ 500 μg/L or with high clinical probability require either a computed tomography pulmonary angiography (CTPA) or a ventilation-perfusion lung scan for definitive diagnosis.

There is good evidence that ‘normal’ d-dimer concentrations physiologically increase with age leading to a lower specificity for PE and more false positives in older patients. In fact, d-dimer testing is able to rule out PE in 60% of patients aged <40 years but only 5% for patients aged >80 years. This results in an increased number of potentially unnecessary and expensive advanced imaging tests in older patients who are also at increased risk of adverse clinical outcomes, such as contrast-induced nephropathy.

An age-specific d-dimer cut-off approach has been suggested, aimed at increasing specificity without reducing sensitivity of d-dimer testing in older populations. Several versions of age-specific d-dimer cut-offs have been described with the most studied being age in years × 10 μg/L which has been recommended for use in recent clinical practice guidelines.

There are also several risk scores in common use, among them the original and simplified Well’s PE score and the original and simplified revised Geneva score. To our knowledge, clinical accuracy of age-adjusted d-dimer cut-offs has not been tested comparing these clinical risk scores.

The objective of this study was to compare the diagnostic utility (sensitivity, specificity and negative predictive value (NPV)) of the age-times-10 age-adjusted d-dimer cut-off when used with the original and simplified Well’s PE score and the original and simplified revised Geneva score to identify patients who are classified as ‘PE unlikely’ according to each score. Score variables and calculation are shown in Table 1.

This was a retrospective cohort study conducted by medical record review of adult patients having both d-dimer and CTPA for investigation of suspected PE. Eligible patients presented to the ED of one of two community teaching hospital ED in Melbourne between 1 January 2012 and 31 December 2015 and were investigated for suspected PE. Patients were excluded if they did not undergo both d-dimer assay and CTPA, if either result was missing or if they were not being investigated for suspected PE. Data were collected from the electronic patient records system and electronic medical imaging system and coded onto specifically designed and piloted data collection forms (I.A., J.M., S.K.). Data collectors were not blinded to study objectives. Data collected included patient demographics, clinical features, data to calculate original and simplified Well’s PE scores and original and modified revised Geneva scores, d-dimer result, CTPA result and final diagnosis. Data definitions were as specified in a pre-designed data dictionary. Patient observations were taken from the first recordings on the emergency observation charts. Where the CTPA result was equivocal, we determined whether PE was present by reference to other investigations, such as ventilation-perfusion lung scan and the opinion of the specialist clinician looking after the patient (A.-M.K.). Inter-rater reliability assessment was performed for 132 cases.

D-dimer level was measured using the Siemens INNOVANCE D-Dimer assay measured on the Siemens/ Sysmex CA-1500 (Siemens/Sysmex, Japan). The age-adjusted cut-off used was 500 μg/L for patients aged 50 and younger and age-times-10 for those aged over 50 years.

The outcome of interest was diagnostic utility (sensitivity, specificity and NPV) for the combination of the defined ‘PE unlikely’ category of each PE risk score combined and d-dimer below the defined age-adjusted cut-off.
off. Analysis was by descriptive statistics and diagnostic utility analysis. The study was approved by the institutional ethics panel. Patient consent for data collection was not required. Six hundred and ten patients met the criteria for inclusion. Median age was 60 years (interquartile range 49–70) and 328 patients were female (53.8%, 95% confidence interval (CI): 49.7–57.8%). Seventy-three patients had a prior history of deep venous thrombosis (DVT)/PE (12% 95% CI: 9.6–14.9%). Overall, the rate of PE was 9.5% (95% CI: 7.4–12.1%). The distribution of classification as low risk by each PE risk score, the conventional d-dimer cut-off and the age-adjusted d-dimer cut-off are shown in Table 2. Of note, an additional 83 d-dimer assay results became classification as low risk by each PE risk score, the conventional d-dimer cut-off <500 μg/L, 82 (13%, 11–16%) patients had a prior history of deep venous thrombosis and low-dose protocols. We have previously reported that compared to the conventional cut-off, use of the age-times-10 cut-off would avoid 21% of further imaging tests. The one missed patient with PE was an elderly lady with sub-segmental PE and a previously undiagnosed lung lesion. Controversy remains about the treatment of such cases in the absence of DVT. It is unclear whether identification of the incidental lung lesion was of benefit to the patient as she has so far declined further testing/follow-up.

Our study has some limitations that should be considered when interpreting the results. Data were collected from medical records so are subject to problems with documentation, particularly omitted data. We did not item’s study eligibility, age, gender, CTPA and d-dimer results.

### Table 2 Score and d-dimer classification as low risk

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Low-risk definition</th>
<th>Number [%]</th>
<th>Sensitivity [%]</th>
<th>Specificity [%]</th>
<th>Negative predictive value [%]</th>
<th>Number of CTPA scans avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Well’s score – original</td>
<td>≤4</td>
<td>564 (92%, 90–94%)</td>
<td>27.9% (24.2–32.0%)</td>
<td>99.3% (95.7–100%)</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Modified Well’s score – simplified</td>
<td>≤1</td>
<td>536 (88%, 85–90%)</td>
<td>28.1% (24.2–32.3%)</td>
<td>99.3% (95.6–100%)</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Revised Geneva score – original</td>
<td>≤4</td>
<td>458 (75%, 71–78%)</td>
<td>28.6% (24.4–33.2%)</td>
<td>99.2% (94.9–100%)</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Revised Geneva score – simplified</td>
<td>≤2</td>
<td>480 (79%, 75–82%)</td>
<td>29.0% (24.9–33.5%)</td>
<td>99.2% (95.2–100%)</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

Note: As scores classified a small number of cases differently, the number of cases classified as low-risk varies by score. CI, confidence interval; CTPA, computed tomography pulmonary angiography.

### Table 3 Diagnostic utility of clinical risk scores combined with age adjusted d-dimer values for low risk patients

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Number of eligible cases</th>
<th>Sensitivity [%] (95% CI)</th>
<th>Specificity [%] (95% CI)</th>
<th>Negative predictive value [%] (95% CI)</th>
<th>Number of CTPA scans avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Well’s original 2-level score</td>
<td>564</td>
<td>97.6% (85.5–99.9%)</td>
<td>27.9% (24.2–32.0%)</td>
<td>99.3% (95.7–100%)</td>
<td>78</td>
</tr>
<tr>
<td>Simplified modified Well’s score</td>
<td>536</td>
<td>97.1% (82.9–99.8%)</td>
<td>28.1% (24.2–32.3%)</td>
<td>99.3% (95.6–100%)</td>
<td>78</td>
</tr>
<tr>
<td>Revised Geneva score – original</td>
<td>458</td>
<td>96.9% (82.0–99.8%)</td>
<td>28.6% (24.4–33.2%)</td>
<td>99.2% (94.9–100%)</td>
<td>64</td>
</tr>
<tr>
<td>Revised Geneva score – simplified</td>
<td>480</td>
<td>97.1% (83.3–99.9%)</td>
<td>29.0% (24.9–33.5%)</td>
<td>99.2% (95.2–100%)</td>
<td>65</td>
</tr>
</tbody>
</table>

Discussion

There is a growing body of evidence that age-adjusted d-dimer cut-offs have acceptable sensitivity for PE and that their use could avoid a significant proportion of CTPA which carry the risk of adverse effects for patients (such as contrast reaction and contrast nephropathy), often cause inconvenience to patients in terms of an extended ED stay and contribute to reduced ED patient flow by requiring an extended ED stay. Age-adjusted d-dimer cut-offs are intended to be used in conjunction with a clinical risk score to identify a group of patients in whom PE is unlikely and therefore further imaging can be avoided. There are sparse data comparing the performance of age-adjusted d-dimer cut-offs with the various risk scores in common use.

Our findings suggest that the age-times-10 age-adjusted d-dimer cut-off has similar accuracy when used with each of the risk scores tested, with point estimate of sensitivity of approximately 97% and NPV >99%. This sensitivity is similar to that reported for CTPA, both standard and low-dose protocols. We have previously reported that compared to the conventional cut-off, use of the age-times-10 cut-off would avoid 21% of further imaging tests.

The one missed patient with PE was an elderly lady with sub-segmental PE and a previously undiagnosed lung lesion. Controversy remains about the treatment of such cases in the absence of DVT. It is unclear whether identification of the incidental lung lesion was of benefit to the patient as she has so far declined further testing/follow-up.

Our study has some limitations that should be considered when interpreting the results. Data were collected from medical records so are subject to problems with documentation, particularly omitted data.
collect data on patients who had a d-dimer but did not go on to advanced imaging, thus very low-risk and some high-risk patients were not included. Limitations of the patient identification systems available meant that we were not able to identify these groups accurately. CTPA reporting was done by a range of general CT radiologists, not specialist pulmonary/thoracic radiologists, so there may be a higher risk of report error than if specialist pulmonary/thoracic radiologists had performed the reporting. However, this reflects the working reality of radiology reporting in most hospitals. The d-dimer test used in this study used fibrinogen equivalent units. Internationally, another unit (the d-dimer unit) is sometimes used which has a different standard cut-off and therefore will have different age-adjusted cut-offs. There is a variety of d-dimer tests available of varying sensitivity. Our findings cannot be assumed to be generalisable to other d-dimer assays, particularly those of lower reported sensitivity.

The age-adjusted d-dimer assay cut-off performed similarly with each of the clinical risk scores tested with high sensitivity and NPV.

References

Levodopa-carbidopa intestinal gel: is the naso-jejunal phase a redundant convention?

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Key words
Parkinson disease, levodopa-carbidopa intestinal gel, treatment initiation.

Abstract
Levodopa-carbidopa intestinal gel (LCIG) is an effective treatment for Parkinson disease. Initiating therapy involves an initial naso-jejunal (NJ) titration phase. The NJ phase is prolonged with significant morbidity. The aim of this study is to assess the impact of proceeding without the NJ phase on resource utilisation and the outcomes of patients. Twenty-five patients were started on LCIG using the patients existing levodopa equivalent dose (LED). We recorded change in LED, length of hospital stay, readmission rates and use of outpatient services and clinical outcomes within 6 months. The median length of stay was 4.5 days. Patients had four outpatient clinic reviews and 2.5 community nurse contacts within 6 months. There was no significant change in daily LED on discharge (P = 0.56). There were significant improvements in all Unified Parkinson Disease Rating Scale subscores (P < 0.05), the Freezing of Gait scale (P < 0.01) and Parkinson Disease Quality Of Life 39 score (P < 0.01). Initiating LCIG without the NJ phase resulted in short admissions, a minimal outpatient burden and no significant requirement for dose titration while producing good clinical outcomes.

Levodopa-carbidopa intestinal gel (LCIG) provides stable plasma levels, giving improved motor symptoms and quality of life compared with intermittent oral dosing in advanced Parkinson disease (PD).1 The recommended procedure for initiating LCIG involves an initial naso-jejunal (NJ) titration phase prior to percutaneous endoscopic gastrostomy-jejunosomy (PEG-J) tube placement for ongoing therapy.2 The NJ phase takes 2–14 days, is often uncomfortable for patients and may predispose to pneumonia.3 We sought to determine whether equivalent clinical outcomes could be achieved if we removed the NJ titration phase and initiated LCIG only after PEG-J tube placement, and whether this effected resource utilisation.

Twenty-five sequential patients who were deemed suitable candidates by a movement disorder specialist and admitted for LCIG initiation between 2013 and 2015 were prospectively assessed. The Alfred Hospital Human Research and Ethics Committee approved this study.

Patients included were clinically diagnosed with advanced idiopathic PD demonstrating a response to levodopa, with severe motor fluctuations (clear ‘off periods’ estimated to last ≥3 h per day and troublesome dyskinesia) on best medical therapy. Cognitive impairment or the presence of neuropsychiatric manifestations of PD was not considered to be contraindication, provided adequate social supports were in place. No patient had previously undergone deep brain stimulation surgery.

All patients provided written, informed consent for initiation of LCIG and underwent the PEG-J procedure on the morning of the first day of admission. LCIG was initiated once appropriate location of the PEG-J was confirmed. The initial LCIG dose was based on the levodopa equivalent dose (LED) pre-procedure medications.3 Dose optimisation involved titration up or down by 0.1–3 mL/h to treat either ‘off’ periods or dyskinesia over the subsequent days. During the admission, the patient and carer received education on the operation of the pump by a specialist nurse. For patients living in residential care facilities, community nurses provided education to the facility’s nursing staff.

We evaluated the change in the LED from the baseline, length of hospital stay, readmission rate, outpatient visit frequency, number of phone consultations and use of community support nurses in the first month after discharge and over the following 5 months.

Assessment scales administered during the ‘ON’ phase prior to LCIG initiation and at 6 months included the

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Conflict of interest: None.

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Unified Parkinson Disease Rating Scale (UPDRS) total and sub-scores (Part I–IV), Freezing of Gait Questionnaire, Epworth Sleepiness Scale (ESS), Montreal Cognitive Assessment and PD Quality Of Life 39 (PDQ39).

Comparisons of outcomes within group at 1 and 6 months were made using paired t-test or Wilcoxon signed rank test as appropriate. Within group changes were assessed and reported with means and 95% confidence intervals. Continuous variables were summarised using mean (standard deviation (SD)) or median (interquartile range (IQR)) as appropriate. Categorical data were reported as number (%). All calculated P values were two-tailed. P value less than 0.05 indicated statistical significance. Analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Twenty-five patients were started on LCIG during the study period. Of this, 22 proceeded directly to PEG-J, and the NJ phase was used initially in three patients. Twenty patients continued on treatment to 6 months. The mean (SD) age was 70.7 (6.9) years, with a slight male predominance (12/22, 54.5%). The median disease duration was 12 years (IQR 10–20).

Median length of stay was 4.5 days (IQR 4–8). Two patients were readmitted. One readmission occurred 3 days post-discharge due to difficulties with gait. The second patient was readmitted at 5 months for management of a stoma site granuloma. The mean number of outpatient reviews was 1.3 (SD 0.8) in the first month and 3.7 (SD 1.8) at 6 months. The community nurse was called upon less than once per patient in the month following discharge and a mean of 2.5 times in 6 months. There was no significant change in the mean LED on discharge when compared to the baseline LED (1655 vs 1594 mg, P = 0.56). There was a slight increase in mean total daily LCIG dose at 1 month when compared to discharge (67.7 vs 69.2 mL, P = 0.047, n = 22). However, there was no further change at 6 months (66.2 vs 67.2 mL, P = 0.15, n = 20).

The mean total UPDRS score at baseline improved by 24% at 6 months (93 vs 70; P = 0.001). The UPDRS Part I improved by 21% (18 vs 14, P = 0.01) and UPDRS Part II scores by 18% (23 vs 19, P = 0.04) after 6 months. Significant improvements were also seen on UPDRS Part III (40 ± 11 to 33 ± 15; P = 0.04) and UPDRS Part IV (12.1 ± 3.5 to 4.4 ± 2.9; P < 0.001). A 24% improvement was seen on the Freezing of Gait Questionnaire (11.9 ± 5.5 to 9.1 ± 5.3; P = 0.007) at 6 months. A similar improvement was also seen in the PDQ39 score at 6 months (67 ± 18 to 53 ± 21; P = 0.005, n = 19). Montreal Cognitive Assessment and Epworth Sleepiness Scale scores remained unchanged (Table 1).

All patients reported short-term abdominal discomfort post-procedure, with no further abdominal complications. One patient suffered a procedural complication with tube-tip location in the proximal duodenum post-procedure. This was treated conservatively and caused a 24-h delay in initiation of LCIG.

During this study, three patients were admitted for a trial of LCIG via NJ tube prior to proceeding to PEG-J tube insertion. The first patient was uncertain about the cosmetics of a PEG-J tube but became convinced of the necessity after an excellent LCIG response during the NJ phase. The second patient was started on LCIG with a NJ phase after abrupt withdrawal of apomorphine infusion therapy due to a cutaneous complication, and a period of delay prior to PEG-J tube insertion. The third patient was given an NJ trial period due to patient uncertainty about

Table 1 Comparison of clinical outcomes at baseline and 6 months follow up (n = 22)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline, mean (SD)</th>
<th>1 month, mean (SD)</th>
<th>6 months, mean (SD)</th>
<th>Difference, mean (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (n = 22)</td>
<td>70.7 (6.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (years) (n = 21)</td>
<td>15.2 (6.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LED, mg (n = 22)</td>
<td>1655 (546)</td>
<td>1594 (682)</td>
<td></td>
<td>61 [-146 to 268]</td>
<td>0.56</td>
</tr>
<tr>
<td>LCIG, mL (n = 22)</td>
<td>67.4 (30.2)</td>
<td>69.2 (30)</td>
<td></td>
<td>-1.5 [-2.9 to -0.1]</td>
<td>0.047</td>
</tr>
<tr>
<td>LCIG, mL (n = 20)</td>
<td>66.2 (31.1)†</td>
<td>67.2 (32)</td>
<td></td>
<td>-1 [-2.4 to 0.4]</td>
<td>0.15</td>
</tr>
<tr>
<td>UPDRS 1 (n = 20)</td>
<td>18 (7)</td>
<td>14 (5)</td>
<td></td>
<td>4 [1 to 6]</td>
<td>0.01</td>
</tr>
<tr>
<td>UPDRS 2 (n = 20)</td>
<td>23 (7)</td>
<td>19 (8)</td>
<td></td>
<td>4 [0.2 to 8.1]</td>
<td>0.049</td>
</tr>
<tr>
<td>UPDRS 3 (n = 20)</td>
<td>40 (11)</td>
<td>33 (15)</td>
<td></td>
<td>7 [0.5 to 13.3]</td>
<td>0.04</td>
</tr>
<tr>
<td>UPDRS 4 (n = 20)</td>
<td>12 (4)</td>
<td>4 (3)</td>
<td></td>
<td>8 [5.6 to 9.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPDRS total (n = 20)</td>
<td>93 (19)</td>
<td>70 (22)</td>
<td></td>
<td>23 [11 to 34]</td>
<td>0.001</td>
</tr>
<tr>
<td>FOG (n = 20)</td>
<td>11.9 (5.5)</td>
<td>9.1 (5.3)</td>
<td></td>
<td>2.8 [1 to 5]</td>
<td>0.007</td>
</tr>
<tr>
<td>PDQ39 (n = 19)</td>
<td>67 (18)</td>
<td>53 (21)</td>
<td></td>
<td>14 [5 to 22]</td>
<td>0.005</td>
</tr>
<tr>
<td>ESS (n = 19)</td>
<td>10.2 (5.3)</td>
<td>10.2 (6.5)</td>
<td></td>
<td>0 [-1.7 to 1.7]</td>
<td>1.0</td>
</tr>
<tr>
<td>MoCA (n = 19)</td>
<td>23.6 (4.7)</td>
<td>24.1 (4.5)</td>
<td></td>
<td>-0.5 [-1.8 to 0.7]</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*Two patients with missing data at 6 months are excluded. CI, confidence interval; ESS, Epworth Sleepiness Scale; FOG, Freezing of Gait; LCIG, levodopa-carbidopa intestinal gel; LED, levodopa equivalent dose; MoCA, Montreal Cognitive Assessment; PDQ, Parkinson Disease Quality of Life 39; SD, standard deviation; UPDRS, Unified Parkinson’s Disease Rating Scale.
potential benefits of treatment. His major concern was back pain, which was perceived to be an ‘off’ phenomenon. He did not proceed to a PEG-J as LCIG did not offer superior symptom relief compared with his oral regimen. The total lengths of these stays were 7, 13 and 3 days, respectively. Of this period, the NJ phase took 4 and 7 days in each of the patients who proceeded to the PEG-J. Two patients who proceeded directly to the PEG-J discontinued. One patient died from a cause not related to treatment 2 months after initiation and the other patient suffered an exacerbation of her anxiety disorders and requested that the PEG-J be removed. This occurred 7 weeks after the treatment was started.

We have shown that LCIG can be successfully initiated in hospital without a NJ titration phase, without any negative impacts on treatment efficacy or resource utilisation. LCIG is a highly efficacious treatment in advanced PD, leading to improvements in motor fluctuations and quality of life. The cost of treatment using LCIG is significantly higher than oral medications, although the benefits are well documented. The cost is partly due to the intensive hospital resources required to initiate treatment, and with our pragmatic approach, hospital stay is minimised without compromising clinical outcome or shifting the burden of care to the outpatient setting.

The early trials of LCIG used the NJ phase to confirm treatment response and then titrate the infusion rate for best clinical outcome before proceeding to the PEG-J. This in-hospital NJ phase may take up to 2 weeks, with the subsequent PEG-J phase taking a further 2–14 days. The mean ± SD time required for dose optimisation in the open-label study was 4.5 ± 2.1 days during the NJ phase and 3.1 ± 2.7 days in the PEG-J phase with a total admission of 7.6 ± 3.4 days. The overall titration time from the double-blind study was 7.1 ± 2.5 days. Our mean admission duration of 5.5 ± 2.4 days compares favourably and suggests merit to our approach. The levodopa total daily dose needed in the open label study remained unchanged between the end of the NJ phase and the end of the PEG-J phase or at the 1-year time point, further emphasising the need for only one titration phase. In the largest LCIG trial of the 354 patients who underwent NJ titration, only five (1%) did not proceed to PEG-J due to perceived lack of efficacy of LCIG. A further 25 (7%) patients were not offered LCIG treatment because of an aborted NJ phase due to multiple factors, including complications of device insertion, oropharyngeal pain and pneumonia. These findings prompted us to adopt the current approach in order to minimise patient discomfort and provide a model for initiation with a shorter hospital admission.

Our findings suggest that the NJ titration may be unnecessary because the baseline-estimated infusion rate (based on pre-LCIG medications) is an appropriate starting dose. This procedure requires very little dose adjustment in the short term, with expected good clinical outcomes. Our median length of stay of 4.5 days (mean of 5.5 days) is substantially shorter than in other studies. Importantly, our approach did not result in readmission due to treatment failure. Equally, our approach compares favourably with a recently published outpatient model, using day procedure PEG-J and clinic-based LCIG initiation and titration 2 weeks later. With that model, the burden of care was shifted from the hospital to the outpatient setting. In our study the use of outpatient resources following admission was not excessive, with adjustments made in outpatient clinics and minor patient concerns or questions handled via telephone advice from specialist nurses.

Our patients were older than in other studies, but recovered well from the procedure and managed the technical aspects of the pump and stoma site wound care. On this basis, older age should not be seen as a contraindication to LCIG. The small size of our study is a recognised limitation, although in this sequential, real-world cohort, the observations compare favourably with larger published reports. We did not study a comparator group with a NJ titration phase as we did not consider this ethical, given appropriate comparison data already published. Finally, we have outlined a successful, streamlined approach to institute LCIG and conclude that improvements in morbidity and reduced hospital stay can be expected if the NJ phase is omitted from standard care.

References

Levodopa-carbidopa intestinal gel: ‘dismantling the road blocks of a journey’

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Abstract

Levodopa-carbidopa intestinal gel offers superior treatment to standard oral therapy in selective patients with advanced Parkinson disease. The costs involved in instituting and maintaining this treatment are high but largely mitigated with the quality of life years the treatment offers. Key to this is ensuring a high retention rate once the treatment is instituted. We outline factors and considerations from our experience and viewpoints at each stage of the process to address in this ‘journey’ patients undertake that can help maximise retention rates and benefits.

After more than 50 years of use, levodopa continues to be the most effective treatment for Parkinson disease (PD). In most patients, levodopa improves motor function by increasing ‘on’ times and reducing ‘off’ times. However, long-term use typically leads to motor fluctuations with troublesome dyskinesias that may require management by a movement disorder specialist. Therapeutic tools to manage motor fluctuations in PD patients include deep brain surgery and device-assisted methods that deliver infusions to maintain consistent levels of dopamine to the central nervous system. Current devices deliver levodopa analogues either subcutaneously (e.g. apomorphine) or through the gastrointestinal tract (e.g. levodopa-carbidopa intestinal gel or LCIG). A recent study of over 900 patients with PD and motor fluctuations initiated on LCIG indicated that the majority (~75%) of patients were able to continue long-term LCIG to achieve improved motor function without troublesome dyskinesias even in the advanced stages of their disease. However, initiating and maintaining this form of treatment is a considerable undertaking, with the caveat that improvements in mobility may also occasionally render the patient at greater risk of falling or developing hallucinations. The costs of LCIG are substantial, but are mitigated by improvements in quality of life years (QALY). However, achieving maximal QALY relies on the durability of treatment benefit. We explore the reasons for discontinuation of therapy seen in up to a quarter of patients, with the aim of maximising retention and thus extending treatment benefits and quality of life.

The process of instituting treatment with LCIG is summarised in Figure 1. Appropriate patient selection and referral to a centre with expertise in LCIG initiation are paramount to optimal treatment response and continuation. It is noteworthy that although moderate to severe dementia is considered a relative contraindication, patients who suffer mild dementia may indeed benefit, and so introduction can be approached with caution. It should be noted, however, that the alleviation of motor symptoms in this subgroup of patients often shifts the emphasis of the disease burden to the cognitive and behavioural aspects of their illness, making these symptoms perceived as more prominent and potentially distressing. Falls and resultant injury may occur more frequently as these patients adjust to their newly found superior motor function. The result may be an unexpected transient worsening of morbidity and quality of life. In addition to improved motor
function in cognitively impaired patients with PD, initiation of treatment with LCIG may also provide benefits for the patient’s carers and healthcare workers, as the improved mobility facilitates the provision of their nursing care.

Optimal procedures to be considered during the treatment initiation phase are related to the method of titration and the insertion of the percutaneous gastrostomy tube with jejunal extension. Titration is typically performed after the insertion of a nasojejunal (NJ) tube. The purpose of the NJ phase in the treatment initiation is to determine whether patients have a favourable response to LCIG. However, results from phase 3 LCIG clinical trials reported that there were no significant dose changes required from one titration phase to another and that the NJ period resulted in both a sizable drop-out and numerous adverse events in its own right.7 Further evidence suggests that with appropriate patient selection and documentation of a convincing levodopa response, no patients experience a lack of efficacy from LCIG if direct insertion of percutaneous endoscopic gastrojejunostomy (PEG–J) is performed.8 Furthermore, the median length of stay was reduced to 4.5 days and outpatient resource utilisation was minimal (mean 1.2 phone consultations and 3.7 outpatient reviews in 6 months) with excellent clinical outcomes achieved.8 There was also no requirement to change significantly the initial LCIG dose at follow-up and no immediate readmissions occurred as a result. An alternative approach of note would be initiation in the outpatient setting.9 This approach may require a separate NJ phase that may last up to four outpatient review days.7 A PEG–J phase follows whereby the PEG–J is inserted on day 1, a subsequent delay in initiation to rest the stoma, then multiple day reviews in a movement disorders centre for titration. While the cost of day reviews would certainly be lower than admissions, this approach is limited by its lack of ability to roll out to diverse healthcare settings worldwide. Access to resource intensive movement disorders services required for this approach is lacking in the majority of non-urban centres around the world. Also, the reproducibility of this approach in private health centres may be challenging. Nevertheless, this approach is worth consideration and remains an alternative approach to initiation of LCIG in a subset of patients.

Procedural considerations to minimise post-procedure complications include using experienced endoscopists for the PEG insertion, minimising tube traction, precise tip placement at the ligament of Treitz to reduce patient discomfort and the need for a general anaesthetic.10 Positioning is typically achieved with a so-called ‘pull’ technique, which requires the recurrent use of an endoscope in optimising the PEG–J position. The adoption of a ‘push’ technique has the advantage of only one endoscopic introduction, thus minimising the risk of complications.10 A radiological jejunostomy approach may also be a worthwhile alternative, obviating the need for the patient to undergo endoscopy.11 While this approach is an attractive alternative to the sizeable wait time for endoscopy some institutions may experience, further clarity on technical differences and outcomes is currently needed before this can be acknowledged as mainstay. A direct endoscopic

Figure 1 Summary of important interventions to minimise discontinuation.
jejunalostomy approach may also be considered as this eliminates the, at times, troublesome fine bore inner tube, which is prone to kinking, migration or being removed by patients.\textsuperscript{12}

Reasons for treatment initiation failure or patient withdrawal are typically related to device-associated complications, worsening cognitive decline, hallucinations or confusion from disease progression and patient dissatisfaction.\textsuperscript{5} Thus, support in the post-procedure phase, particularly in the first 3 months,\textsuperscript{13} is essential to minimise the proportion of patients discontinuing due to surgery-related complications and device issues, such as tube occlusion and stoma infection.\textsuperscript{3} Patients may also discontinue as a result of poor caregiver compliance.\textsuperscript{5} This is due to carers’ expectations not being met and poor understanding of management requirements resulting in suboptimal outcomes. Access to a well-developed movement disorder service with a professional, skilled and committed team of movement disorders specialists and specialist nurses well educated on LCIG-related care is crucial.\textsuperscript{6} Follow-up sessions to ensure optimal function and a structured daily routine are also helpful.

Aftercare ensuring compliance adherence to basic post-procedure care, such as a gradual introduction of solid foods, early painkiller administration, appropriate tension between internal and external retention plates and fixation of PEG/J to the skin, is critical and assists in minimising discontinuation due to device-related concerns. Daily stoma inspection, cleaning and flushing, tube mobilisation (push and pull not rotation) should be performed by carers or patients to reduce device-related complications. Access to clinic or phone consultations with healthcare professionals provides reassurance to both patients and carers and may also reduce the risk of discontinuation. Other important support measures to maintain continuation include follow-up rating scales to provide objectivity in treatment decisions, regular pump checks, written checklists and links to support groups.\textsuperscript{10}

LCIG is a highly efficacious treatment for a broad range of PD patients, inclusive of those affected by mild cognitive impairment. A degree of flexibility in approach to each individual’s needs may be necessary to achieve the best outcomes for each patient. Treatment considerations transcend a lengthy journey and require long-term support from a centre with expertise from a multidisciplinary team.

References

LETTERS TO THE EDITOR

Clinical-scientific notes

Symptomatic hypereosinophilia associated with Necator americanus self-inoculation

A 2006 systematic review found that, in populations with endemic hookworm infection, there was a reduction in long-term asthma risk in those who were infected, compared with those who were not. However, no benefit of helminthic therapy in previously uninfected patients with asthma and other allergic diseases has been demonstrated in several studies. A 2012 Cochrane review of helminthic therapy for allergic rhinitis showed no significant reduction in overall medication use, although there was less use of rescue medication in one study using pig whipworm. Despite this lack of evidence, the treatment is marketed online for a plethora of autoimmune, inflammatory and uncategorised conditions. As a cautionary tale, we present here the first report of organ damage due to hypereosinophilia after deliberate helminth infection used in an attempt to modulate allergic symptoms.

A man in his early 60s presented to an Emergency Department with palpitations and was found to have atrial fibrillation with a ventricular rate of 120–180 bpm. Reversion to sinus rhythm occurred after treatment with adenosine. He had a mild elevation in troponin I of 0.75 μg/L (<0.03), which remained stable on serial measures and was presumed to be secondary to the arrhythmia. A chest radiograph revealed a small left pleural effusion with ipsilateral lower zone patchy peri-bronchial infiltrates. He was stable overnight with cardiac monitoring and discharged home with beta-blocker therapy, and was now elevated to 1.9 μg/L (<0.03), and in left ventricular function. An echocardiogram performed at this time showed normal LV size and systolic function, normal RV size and systolic function, and borderline left atrial enlargement.

At this stage a persistent eosinophilia (≈10 × 10^9/L (<0.7)), present since his first presentation, was noted. Further questioning revealed the patient had self-initiated inoculation with Necator americanus (New World hookworm) parasites, obtained online, to treat his asthma and allergic rhinitis. Inoculation was performed three times transdermally according to the supplier’s advice: an initial dose of 35 parasites 9 months prior to presentation, a second dose of 50 parasites 4 months prior, and most recently 50 parasites 7 weeks prior. His pretreatment IgE was 248 kU/L (<100) and eosinophil count 0.6–1.15 × 10^9/L, last measured 9 months prior to his current presentation. Other relevant test results at presentation are shown in Table 1.

A provisional diagnosis of eosinophilic damage to the myocardium and Loeffer’s syndrome affecting the lungs (rather than a community-acquired pneumonia) was made. An acute eosinophilic myocarditis was the presumed cause of the elevated troponin level and arrhythmias seen in this patient. Other differential diagnoses considered included eosinophilic granulomatosis with polyangiitis – previously known as Churg-Strauss syndrome – (due to the patient’s history of asthma, sinusitis and nasal polypectomy 3 years prior), idiopathic hypereosinophilia, and an eosinophilia secondary to a haematological malignancy. As shown in Table 1, tests relevant to these diagnoses were negative. There was no other past medical history, and prior to presentation the patient was taking only medications for asthma and sinusitis. There was no recent history of travel but 30 years prior the patient had been treated for a parasitic gastrointestinal infestation while working in the Northern Territory, Australia. At that time, he had also travelled extensively around Asia and Europe.

At the time of this presentation, he had no gastrointestinal symptoms and stool cultures were negative (collected within 72 h of treatment commencement). His equivocal and subsequent positive Strongyloides serology was attributed to cross-reactivity with hookworm with the Strongyloides ratti L3 larvae crude extract used in the enzyme immunoassay test (personal communication with testing laboratory). The Harada-Mori
technique was used as a more sensitive examination for the presence of *Strongyloides* and was negative.4

Given the potentially fatal condition of eosinophilic myocarditis5 and that an endomyocardial biopsy for definitive diagnosis of the condition was not immediately available, we decided to treat the patient presumptively with albendazole and a short course of prednisolone tapering from 25 mg to lower acutely the eosinophil count to prevent further damage. Echocardiography is typically normal during the early, necrotic stage of eosinophilic myocarditis,6 and so we did not feel that the relatively normal echocardiography negated our provisional diagnosis. The pulmonary infiltrates, symptomatic chest pain and eosinophilia promptly resolved over 2 days. Twelve months after his initial presentation, the patient remains well, has a normal eosinophil count and there has been no long-lasting cardiac damage.

An inoculum of 10 *N. americanus* larvae has been shown to give the level of infection seen in epidemiological studies.7 Although this level of inoculum failed to show significant benefits for asthma control, a study did demonstrate eosinophil counts of up to $8.5 \times 10^9$ without serious side-effects at 12 weeks of follow up, at which time the infection was eradicated.8 There are no other reports in the literature of organ-damaging eosinophilia after helminthic therapy to our knowledge. This is in contrast to our patient who took a significantly larger number of larvae and over a longer time, possibly accounting for the serious adverse events seen in this case. Our case highlights the importance of recent research to identify particular proteins secreted by helminths that may have an immune modulatory effect without requiring infection with the helminths themselves.9 It also serves as a caution and highlights the potential harms of helminthic treatment when hypereosinophilia results.

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**Table 1** Blood test results at presentation

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC Hb 122 g/L (135–180), WCC 19.8 x 10^9/L (4–11), Eosinophils 9.88 x 10^9/L (0–0.7), Neutrophils 7 x 10^9/L (1.8–7.5), platelets 341 x 10^11/L (150–400)</td>
<td></td>
</tr>
<tr>
<td>EUC Normal</td>
<td></td>
</tr>
<tr>
<td>LFT Normal</td>
<td></td>
</tr>
<tr>
<td>ESR 20 mm/h (&lt;30)</td>
<td></td>
</tr>
<tr>
<td>CRP 10.2 mg/L (&lt;5.0)</td>
<td></td>
</tr>
<tr>
<td>B and T cell subsets Normal</td>
<td></td>
</tr>
<tr>
<td>ANCA Not detected</td>
<td></td>
</tr>
<tr>
<td>ANA 1:80 titre, speckled pattern</td>
<td></td>
</tr>
<tr>
<td>ENA Negative</td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA 4 IU/mL (&lt;40 IU/mL)</td>
<td></td>
</tr>
<tr>
<td>Complement levels C3 1.14 g/L (0.82–1.85), C4 0.20 g/L (0.14–0.42)</td>
<td></td>
</tr>
<tr>
<td>IgE level 359 KU/L (&lt;100)</td>
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</tr>
<tr>
<td>Other immunoglobulin levels IgG, 14.6 g/L (7–16); IgA, 1.53 g/L (0.70–4.00); IgM, 0.8 g/L (0.4–2.3)</td>
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</tr>
<tr>
<td>Tryptase 7.1 μg/L (0.9–11.4)</td>
<td></td>
</tr>
<tr>
<td>Strongyloides serology (IgG ratio) At presentation: 1.06, indeterminate (&lt;0.80, negative), 6 months post presentation: 2.25</td>
<td></td>
</tr>
<tr>
<td>Stool ova, cysts and parasite examination Negative x 3</td>
<td></td>
</tr>
<tr>
<td>Harada-Mori fresh stool examination Negative x 3</td>
<td></td>
</tr>
<tr>
<td>HIV Not detected</td>
<td></td>
</tr>
</tbody>
</table>

Bold indicates values outside the normal range. ANA, anti-nuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; CRP, C-reactive protein; dsDNA, double-stranded DNA; ENA, extractable nuclear antigens; ESR, erythrocyte sedimentation ratio; EUC, electrolytes urea creatinine; FBC, full blood count; Hb, haemoglobin; HIV, human immunodeficiency virus; LFT, liver function tests; WCC, white cell count.
Ibrutinib and antimicrobial therapy in a heavily pretreated patient with chronic lymphocytic leukaemia and disseminated cutaneous non-tuberculous mycobacterial infection: successful surgery-free approach

Chronic lymphocytic leukaemia (CLL) is a monoclonal B-cell lymphoproliferative disorder characterised by the accumulation of small, mature B cells in the peripheral blood, lymph nodes, liver and spleen. Susceptibility to infection remains a significant cause of morbidity and mortality due to well documented immunological defects seen in CLL, particularly T-cell dysfunction, as well as the immunosuppressive effects of therapy. Novel agents targeting B-cell receptor signalling, such as the Bruton tyrosine kinase inhibitor ibrutinib, are emerging as promising therapies in patients with CLL either as monotherapy or in combination with other treatments, such as monoclonal antibodies. While infection is a common early complication, emerging data suggest ibrutinib therapy may ultimately overcome the ‘T-cell’ defect in CLL leading to the potentiation of antitumour immune responses and reduced predisposition towards infection.

In March 2015, a 68-year-old male with heavily pretreated CLL presented with a 6-month history of multiple violaceous nodules over his right leg, left wrist and both hips (Figs 1, 2). In retrospect, these lesions had been originally observed 3 months earlier in June 2014 as non-raised ‘purpuric’ lesions thought to represent areas of bruising related to ongoing immune thrombocytopenia complicating his CLL. Following his original diagnosis in 2003, the patient’s previous treatment history included oral chlorambucil, two separate courses of FCR (fludarabine, cyclophosphamide, rituximab) in 2006 and 2009, alemtuzumab, the bcl-2 inhibitor venetoclax and finally R-CHOP ((rituximab, cyclophosphamide, vincristine, doxorubicin and prednisolone)) with involved field radiotherapy for localised Richter transformation in 2013. In addition, the patient was receiving monthly intravenous immunoglobulin (IVIg) to prevent recurrent respiratory tract infections complicating hypogammaglobulinaemia as well as intermittent rescue doses of IVIg for management of his idiopathic thrombocytopenic purpura, but no other systemic treatment for his CLL. During 2014, the patient experienced clinical and radiological progression of his CLL and the previously noted ‘purpuric’ skin lesions developed further into raised, linear lesions thought to represent thrombophlebitis, which was excluded on ultrasound examination. The lesions continued to grow in size in the lead-up to commencing ibrutinib in November 2014 for progressive CLL, which subsequently results in a partial remission without associated toxicity. At the time of presentation, his trough immunoglobulin levels were satisfactory on IVIg and he had a normal neutrophil count. While awaiting diagnosis, the patient continued on ibrutinib for 5 months, remained systemically well and the lesions demonstrated early signs of regression (Figs 2, 3). Punch biopsies of lesions from the wrist and left leg demonstrated dermal suppurrative granulomatous inflammation with acid-fast bacilli consistent with mycobacterial infection. Mycobacterial culture and polymerase chain reaction identified Mycobacterium cheloneae with sensitivity only to clarithromycin, azithromycin and tigecycline. Following identification of underlying mycobacterial infection, azithromycin and doxycycline antimicrobial therapy was commenced leading to further clinical improvement...
such that formal surgical excision was not required. Antimicrobial therapy was discontinued after 18 months and the lesions remain healed with no evidence of infection reactivation 7 months after cessation of antibiotics (Figs 4, 5).

Two important and noteworthy clinical observations arise from this case. First, our case represents one of only a handful of reported cases of cutaneous, non-tuberculous mycobacterial infection in a patient with CLL emphasising the importance of considering this unusual infection in the differential diagnosis of skin lesions in heavily pretreated CLL patients. Second, the improvement in skin lesions seen on ibrutinib while undergoing investigation and prior to initiation of effective antimicrobial therapy suggests ibrutinib may indeed have similar immune reconstituting properties as postulated to occur with lenalidomide treatment in a case report of *Mycobacterium marinum* infection.5

Cutaneous *M. chelonae* infection is a notoriously difficult infection to eradicate that usually requires not only prolonged multidrug therapy with antimicrobials to which the organism is sensitive, but also surgical excision of infected lesions.6 In our case, resolution of lesions occurred despite treatment with only one antibiotic to which the organism was sensitive *in vitro* (azithromycin) and without adjunctive surgical excision. Infection is a well described early complication in ibrutinib-treated CLL patients and appears to abate...
with prolonged therapy. Our case adds to the growing number of case reports documenting outcomes of atypical infection in ibrutinib-treated CLL and lymphoma patients. We believe that our unique case further stimulates interest in the hypothesis that ibrutinib therapy over time may lead to immune reconstitution and activation, which may result in reduced infection-related morbidity and mortality.7,8

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References

Figure 4 After 18 months of antibiotic treatment – right leg.

Figure 5 After 18 months of antibiotic treatment – left wrist.
**Back pain and fever: when the diagnosis becomes crystal clear**

In April 2015, a 61-year-old man presented to a tertiary hospital in Melbourne, Australia, with generalised weakness and left knee pain. He had a past history of type-2 diabetes and gout. Clinical examination revealed a warm, tender left knee with effusion. Laboratory findings included an elevated serum uric acid 679 μmol/L (normal 180–420 μmol/L), C-reactive protein (CRP) 215 mg/L (normal 0–5 mg/L) and creatinine 138 μmol/L (normal 66–105 μmol/L). Joint aspirate of the left knee revealed monosodium urate crystals. Prednisolone (50 mg/daily) resulted in symptomatic and biochemical improvement. Allopurinol (50 mg/daily) was introduced on day 17 while prednisolone was tapered. Over the following fortnight, he developed worsening thoracolumbar back pain associated with episodic pyrexia and hypotension.

Pertinent laboratory findings included CRP up to 329 mg/L. Serology and cultures of blood, urine and cerebrospinal fluid were unremarkable. Immunological tests were normal. Whole body computed tomography (CT) was non-diagnostic. Magnetic resonance imaging (MRI) spine demonstrated enhancement in the left L3/4 and L4/5 facet joints, suggestive of septic facet joint arthritis. Subsequent CT-guided aspirates from the facet joints did not yield any pathogens. Empiric intravenous ceftriaxone and vancomycin over a fortnight did not result in any clinical improvement.

In an attempt to obtain a microbiological diagnosis, all antimicrobials were ceased. The patient remained febrile and multiple blood cultures remained sterile. An 18F-fluorodeoxyglucose positron emission tomography scan demonstrated multiple joint inflammations suggestive of polyarticular gout (Fig. 1). An aspirate of the right acromio-clavicular joint confirmed monosodium urate crystals. The patient was commenced on high-dose colchicine resulting in rapid improvement over a fortnight. He became afebrile and inflammatory markers normalised. On review in August 2015, the patient remained clinically stable, afebrile and undergoing rehabilitation.

![Image of 18F-Fluorodeoxyglucose positron emission tomography/computed tomography (CT) scan demonstrating intense periarticular glycolytic activity involving multiple bilateral joints.](image-url)
The clinical spectrum of acute gout includes pain, erythema and swelling of a single or multiple joints, and may be accompanied by pyrexia and leukocytosis. Gout typically affects the lower extremities; however, a recent study suggests 14% involves the axial skeleton. Similar to our case, the facet joints of the lumbar spine were found to be the most commonly affected area. Tophaceous gout of the spine may be difficult to differentiate from spinal osteomyelitis as their appearances may be similar on MRI and CT.

This case illustrates acute polyarticular gout presenting with back pain and systemic inflammatory response syndrome (SIRS). Mouse models have demonstrated monosodium urate crystals can trigger a release of cytokines. Previous reports of polyarticular gout presenting with SIRS describe involvement of the extra-axial joints rather than the spine.

We present this case to highlight axial involvement in polyarticular gout is not uncommon and has the ability to induce a SIRS reaction. To establish the underlying cause of SIRS, careful history taking, examinations and targeted investigations for infectious and non-infectious processes are warranted. Multilevel spinal infection is unusual and therefore non-infectious aetiologies should be considered. Given the clinical and radiological difficulty in distinguishing polyarticular gout-related SIRS from sepsis caused by septic arthritis or osteomyelitis, the importance of examining synovial fluid with polarised light microscopy should not be underestimated.

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Anti-type M phospholipase A2 receptor antibody-positive membranous nephropathy as a part of multi-system autoimmune syndrome post-allogeneic stem cell transplantation

A 50-year-old man with myelodysplasia underwent a matched-unrelated allogeneic stem cell transplantation (ASCT) with fludarabine-busulphan-thymoglobulin conditioning. Initial post-transplant period was uneventful and he was discharged on D + 25 (Fig. 1, top).

On D + 75, he represented with lower limb weakness and was subsequently diagnosed with autoimmune transverse myelitis, on the grounds of characteristic radiological findings and a lumbar puncture with raised protein, lymphocytosis and a negative microbiological work-up. He achieved neurological remission with immunosuppressive therapy. Around D + 90, he developed nephrotic syndrome with gross peripheral oedema and a 20-kg weight gain (Fig. 1, bottom). This was associated with acute kidney injury (serum creatinine 179 μmol/L, baseline: 88) and hypoalbuminaemia (serum albumin: 17 g/L, reference range (RR): 35–45).

Protein-to-creatinine ratio was raised at 1192 mg/mmol (RR: <15). Concurrently, he developed Evans Syndrome (direct Coombs’s test positive) with anaemia (Hb: 450 μmol/L, RR: 130–180) and severe thrombocytopenia (platelet: 8 × 10^9/L, RR: 150–450), contraindicating a renal biopsy. Anti-type M phospholipase A2 receptor (anti-PLA2R) assay returned strongly positive – consistent with a diagnosis of autoimmune membranous nephropathy. Definitive management with rituximab (375 mg/m^2 weekly) for 4 weeks was given with excellent response after treatment resistance with high-dose corticosteroids. Throughout this admission, he demonstrated no evidence of graft-versus-host disease (GvHD) and was subsequently discharged on D + 150 on maintenance cyclosporine 100 mg twice daily.

At 8 months post-ASCT, his renal function had normalised (serum creatinine: 76 μmol/L) with a negative serum anti-PLA2R test. He exhibited full donor chimerism and he was off immunosuppression, with no evidence of chronic GvHD.

ASCT-associated autoimmunity is thought to be due to chemotherapy-induced regulatory T-cells depletion and self-reactive T-cells expansion during haemopoietic reconstitution. While haematological and neurological

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compromise are common, nephrotic syndrome is uncommon and often (but not always) occurs in the context of chronic GvHD. Membranous nephropathy accounts for approximately 60% of cases and portends a worse renal prognosis. Unfortunately, renal biopsy may not always be clinically feasible here, co-existing thrombocytopenia was a contraindication. In such scenario, the serum anti-PLA2R assay is particularly useful; it is highly specific (100%) and sensitive (75%) for autoimmune membranous nephropathy and can also be used to follow up treatment responses, as its serum titre correlates with disease activity.

Specific therapy for ASCT-associated autoimmune membranous nephropathy is an evolving landscape. In our patient, proteinuria was slow to resolve with high-dose corticosteroids, hence the decision to introduce rituximab, which markedly improved his renal parameters. We await with great interest his long-term renal outcome, as long-lasting renal remission by employing rituximab as salvage therapy has been reported previously. Encouragingly, 8-months later, his renal function had normalised and serum anti-PLA2R titre was correspondingly negative.

This case highlights the diagnostic and prognostic utility of the anti-PLA2R assay for autoimmune membranous nephropathy in the context of multi-system autoimmune syndrome post-ASCT. A positive result may justify the exclusion of renal biopsy for timely diagnosis and treatment decision. Additionally, serum anti-PLA2R titre correlation with disease activity is useful for following up response to therapy. Finally, our case also demonstrates the efficacy of rituximab in treating steroid-resistant autoimmune membranous nephropathy, specifically in the post-ASCT setting.

Received 16 April 2017; accepted 27 December 2017.

Aditya Tedjaseputra, † Donal McLornan, Jill McCormick, Kavita Raj, Hugues de Lavallade, Victoria Potter, Michelle Kenyon, Antonio Pagliuca, Judith Marsh and Ghulam Mufti
Breathlessness and palliative oxygen therapy in advanced chronic obstructive pulmonary disease

We recently reported in the Internal Medicine Journal that junior doctors report high awareness, confidence, willingness and experience prescribing opioids to chronic obstructive pulmonary disease patients with refractory breathlessness.1 However, opioids are only the final step in a comprehensive management plan, which should first include non-pharmacological strategies, such as smoking cessation, self-management education, physical activity, pulmonary rehabilitation, breathing exercises and the use of a handheld fan.2-4 In this letter, we describe junior doctors’ knowledge and views regarding these strategies and palliative oxygen therapy (POT).

From the 223 full-survey responses received, there was limited recommendation of non-pharmacological strategies for refractory breathlessness, with the three most commonly recommended being pulmonary rehabilitation (30.0%), using a handheld fan (14.8%), and anxiety management and relaxation techniques (13.0%). Similarly, very few trainees recommended multidisciplinary input from nursing or allied health professionals such as community nurses (3.6%) or physiotherapists (8.1%), and only 6 (2.7%) recommended patient and carer education to reduce breathlessness.

Approximately, half of the respondents (116, 52.0%) believed that POT (i.e. oxygen therapy used at rest in patients who do not qualify for long-term oxygen therapy) relieved refractory breathlessness in patients who do not have severe hypoxaemia, while 45 (20.2%) were unsure. Twelve trainees indicated that oxygen might improve dyspnoea by reducing anxiety or by having a placebo effect. The belief that oxygen relieves refractory breathlessness was not associated with any trainee demographic characteristics.

These findings may be explained by the trainees’ early career stage and the fact that they predominantly work as part of a consultant-led team managing inpatients. In that setting, there is ready access to an expert, multidisciplinary team including physiotherapists and occupational therapists, who can educate patients regarding self-management and non-pharmacological breathlessness strategies. Thus, the medical team may be more focused on diagnosis and prescribing appropriate medications for refractory breathlessness. Additionally, trainees may assume that similar structures of multidisciplinary care are in place and accessible in the community.

Recent studies suggest that POT is burdensome and does not improve refractory breathlessness, quality of life or survival.5,6 However, in a small minority of patients POT may relieve breathlessness, therefore oxygen prescription must be individualised.7 Physicians are divided as to the benefits of POT, with 58% of respiratory physicians and palliative care specialists in Australia and New Zealand surveyed in 2005, believing that POT is beneficial.8 Given the similar results in our recent study,

References


doi:10.1111/imj.13748
disappointingly the latest evidence has not translated into clinical knowledge. Surveys are challenging as respondents have to choose definitive answers to clinical questions, which in reality require cautious evaluation for individual patients. Similarly, participants may make implicit assumptions regarding clinical management, when responding to case vignette scenarios. However, our findings suggest that Australian junior doctors focus on pharmacological treatments and oxygen for refractory breathlessness, and they have less awareness of the evidence-based, multidisciplinary, non-pharmacological interventions, which come first in clinical practice. Further education regarding refractory breathlessness management, and particularly using a comprehensive, stepwise approach, is required to translate evidence into practice.

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References


The unique aspects of chronic hepatitis B infection in Aboriginal and Torres Strait Islander people

We commend Mohsen and Levy for the recent publication of their excellent review, ‘Hepatitis A to E: what’s new?’ in the Internal Medicine Journal. We acknowledge the breadth of this topic and that not everything could be covered in the space allocated. We would like to complement their article by highlighting the disproportionate burden of chronic hepatitis B (CHB) that is borne by Aboriginal and Torres Strait Islander Australians (from herein respectfully referred to as Indigenous Australians).

Indigenous Australians make up 2.5% of the national population but comprise 9.3% of those with CHB. Their risk of hepatocellular carcinoma (HCC) is six times that of the non-indigenous population and contemporary estimates of HBsAg positivity for Indigenous Australians in the Northern Territory (NT) are 6.08%.[2] Uniquely, all Indigenous Australians living with CHB in the NT whose virus has been molecularly examined have been shown to have the otherwise uncommon sub-genotype C4.[3] HBV/C4 has genotypic markers that are associated with rapid progression to cirrhosis and HCC and also a different serotype (ayw3) to the vaccine genotype A2 (ayw2) used in Australia. The implications of these genotypic markers of virulence and serotype mismatch with the vaccine (e.g. potentially reduced efficacy) require further study.

Based on this demonstrated high risk of HCC,[3] in collaboration with the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) and the Central Australian Rural Practitioners Association, we have adapted the HCC screening table from the American Association for the Study of Liver Disease guidelines.

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that was presented in Mohsen and Levy’s review to include Indigenous Australians over the age of 50 (Fig. 1). In the Australian context, this is an important addition and is freely available on ASHM’s website.8

We concur with Mohsen and Levy regarding the confusing terminology used to describe the different phases of CHB and we found that the simplified terms proposed in their table 2 provided some clarity. We note although that qualitative work carried out in a remote northern Australian Indigenous setting has raised concerns about the use of the word ‘silent’ (phase 1 in table 2) to describe the early phases of hepatitis B as it is commonly misinterpreted to mean that the condition resulted from sorcery.7 In an effort to achieve a shared understanding with our Indigenous Australian patients, we have started to refer to the phases simply as ‘one’, ‘two’, ‘three’ and ‘four’, which we support through the use of a bilingual app.10 This aligns with research showing that a shared understanding between patient and care provider is a prerequisite to sustainable and quality engagement in care.9

The hepatitis B virus was first identified from the blood of an Indigenous Australian,11 and liver disease is the third most important contributor to the gap in life expectancy still being experienced by Indigenous Australians.12 Broad recognition of the higher burden and higher risks of CHB in this setting is an important first step to improving this situation.

Received 19 September 2017; accepted 2 October 2017.

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9 Davies J, Bukulatjpi S, Sharma S, Davis J, Johnston V. “Only your blood can tell the story” – a qualitative research study using semi-structured interviews to explore the hepatitis B related knowledge, perceptions and experiences of remote dwelling indigenous Australians and their health care providers in northern Australia. BMC Public Health 2014; 14: 1233.
12 Australian Institute of Health and Welfare. Contributation of Chronic Disease to the Gap in Adult Mortality between Aboriginal and Torres Strait Islander and Other Australians. Canberra: The Institute; 2010.
Author reply

We thank Davies et al. for their letter providing readers with useful additional insights about chronic hepatitis B virus (HBV) infection in the Aboriginal and Torres Strait Islander People for our article ‘Hepatitis A to E: what’s new’. It was an oversight not to include comment on this important population, whose needs have been critically highlighted in the recent article by Parker et al., which describes the relatively high incidence and poor outcome of hepatocellular cancer (HCC) in indigenous people of the Northern Territory. Indigenous Australians tend to present late and outside of surveillance programmes with individual annual HCC risk, in HBV-infected indigenous people, 0.34% for ages 50–59 and 0.83% for ages 60–69. Median maximum tumour size at diagnosis 8 cm suggests tumours had been present for some time. We thank the authors for pointing out the issue, but we see no evidence to support their suggestion that ASHM recommendation for surveillance beginning at only age 50 is of merit. Those ‘recommendations’ in a flyer on the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) website are not supported by any evidence, professional societies or guidelines. In fact, there are multiple reasons why we believe age 50 would be too late. First, if the goal is to identify a small and treatable tumour, then screening 10 years before when the tumours start, thus at age 40 at least, would make more sense. We do not have enough information to recommend different starting points based on gender, like we currently do for Asians. That 40% of the HCC occurred in indigenous women suggests this would be unwise too. Possibly, recommendations for Africans for screening to commence at age 20 should apply. Further research is required.

The perceptions Indigenous Australians have about the term ‘silent’ in our simplified terminology for the HBV phases are of interest. A qualitative study reported the term silent might be misinterpreted to mean from sorcery, which would give the wrong impression about the indolence of this particular phase of HBV. However, as sorcery is commonly held responsible for disease perhaps this concept will pervade perceptions regardless of the terminology. Numerical representation to identify phases are not well retained by health consumers in our experience, so have less use when trying to engage consumers in a long-term healthcare journey. The visual imagery of the Hepatitis B Bear achieves retention of concept and meaning and is culturally acceptable to a diverse population in our experience and when recently tested in Kings College London (publication pending abstract presented AASLD 2017).

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5 Davies J, Bukulatji S, Sharma S, Davis J, Johnston V. ‘Only your blood can tell the story’ – a qualitative research study using semi-structured interviews to explore the hepatitis B related knowledge, perceptions and experiences of remote dwelling indigenous Australians and their health care providers in northern Australia. BMC Public Health 2014; 14: 1233.

Author reply

We thank Currow et al. for their interest in the survey of Australian junior doctors regarding beliefs and attitudes to managing refractory breathlessness in patients with severe chronic obstructive pulmonary disease undertaken by Smallwood et al. However, as Currow et al.’s letter principally concerns the Cochrane review regarding the utility of opioids for refractory breathlessness undertaken by Barnes et al. and on which Smallwood is a co-author, in this letter we would like to respond to Currow et al.’s opinion that the Cochrane review contained methodological flaws. Their criticisms...
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were published last year in the feedback section of our Cochrane review, as was our full response with evidence that their assertions were unfounded.3 However, given the serious and ongoing nature of the criticisms now published in the Internal Medicine Journal, we think it is important to summarise our response here.

First, there is not one ‘standard method’ for incorporating crossover data into meta-analyses,1 instead the Cochrane Handbook outlines several possible methods, including using the data as if it was a parallel study, which was the method first used in our Cochrane review.1,4 We also conducted a sensitivity analysis with a meta-analysis using correlation coefficients and corrected standard errors (as an alternative method to include crossover data). The results of the original analysis and new sensitivity analysis were not dissimilar, thus were consistent with our previous conclusion.3

Second, Currow et al. raise concerns regarding the use of a fixed effects model versus a random effects model.1 The a priori choice and rationale for a fixed effects model was outlined in advance in the protocol, which was peer reviewed prior to publication.3 Both fixed effects and random effects models were presented in the sensitivity analyses, and found no differences in effect.3

Third, Currow et al. suggested that we downgraded the quality of evidence based on concerns about study size alone.1 We used GRADE methodology to rate the quality of the evidence and our decision to downgrade the quality of the evidence was based on the fact that more than 50% of the included trials did not report on allocation concealment, blinding of participants or personnel or blinding of outcome assessment.3 This is a potential serious limitation when the primary outcome (i.e. change in breathlessness) is entirely subjective. We acknowledge that study size per se does not influence the internal validity of trial results and that some of the trials included in the review were designed with sufficient statistical power. Additionally, the ‘size bias’ criterion was suggested by the Cochrane editorial team during the review process of our manuscript, as there is empiric evidence that study size may be a surrogate marker of trial quality when the reporting on aspects of trial quality is poor.5

As the additional sensitivity analyses do not change the original Cochrane review conclusions,3 we strongly disagree with the repeated assertions made by Currow et al. of flawed methodology.1,3 There is some small, low-quality evidence that shows a modest benefit from the use of parental or oral opioids to palliate breathlessness in the short term. Notably, long-term studies and evidence suggesting an improvement in quality of life are lacking.7 As such further studies are required, particularly given the risks of adverse events.

The Cochrane review process is recognised to be world class in providing robust systematic reviews and meta-analyses, which are essential for supporting evidence-based practice for busy clinicians. A meta-analysis conducted without the context of this rigorous review process should be interpreted with caution and does not strengthen the evidence for the use of opioids for breathlessness.

Acknowledgements

We thank Dr Christopher Cates (Cochrane Airways Review Group) for his extensive input on the sensitivity analyses and comments on our previous response, Dr Kerry Dwan (Cochrane Editorial Unit), Mr Toby Lasser son (Cochrane Editorial Unit) and the Cochrane Statistical Methods Group, and Professor Julian Higgins (University of Bristol) for his report on the interpretation of this data.

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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 Thomas Shultz should be Thomas Ray Schulz.

The authors of the article should thus be:

Justin T. Denholm, Emma S. McBryde, Damon Eisen, Alan Street, Elizabeth Matchett, Caroline Chen, Thomas Ray Schulz, Beverly Biggs and Karin Leder.

The authors apologise for the error.
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